U.S. PATENT APPLICATION

for

Narcotic-NSAID Ion Pairs

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Narcotic-NSAID Ion Pairs

BACKGROUND OF THE INVENTION

[0001] The present invention relates generally to the field of new drug therapies that encompass at least one narcotic and at least one NSAID chemically united as an ion pair.

[0002] Many conventional therapeutic regimens rely upon combination therapies, that is, the co-administration of two or more drugs, that often result in certain enhanced therapeutic effects that could not be achieved with a single drug. Positive pharmacodynamic interactions between the drugs in this regard thus fall generally into two broad categories. Two co-administered drugs with similar actions may simply yield an additive effect, essentially evaluated as the sum of the therapeutic effects of the individual drugs. For example, aspirin and codeine are often given together to enhance pain relief.

[0003] Second, when two or more drugs are co-administered, one drug may exhibit a synergistic effect on the other drug. That is to say, the combined therapeutic effect of both drugs is greater than the sum of the therapeutic effects ascribed to the individual drugs. A significant advantage in this regard is that lower dosages of one or more of the drugs may result. To illustrate, in a meperidine (a narcotic analgesic) and promethazine (an antihistamine) combination, promethazine enhances the effect of meperidine, thereby allowing the practitioner to administer lower doses of the narcotic.

[0004] Combination therapies, as outlined above, present a number of disadvantages. First, as the description implies, combination therapy implicates the administration of at least two drugs, thereby requiring a patient to accept multiple and/or larger dosage forms of the drugs. Such therapies require careful mixing of the drugs to ensure accurate doses of each drug. Scenarios in which the drugs may exhibit *negative* additive or synergistic effects prescribe additional care to achieve the correct relative dosages and thereby avoid potential adverse effects. Additionally, multiple doses tend to strain patient compliance, particularly among the pediatric and

geriatric populations. Thus it would be desirable to co-administer two or more drugs in a single dose in controlled, if not rigorously fixed, proportions.

[0005] Second, a substantial subset of drugs is salts or salt prodrugs that, as a consequence of their ionic nature, greatly facilitate their water solubility and resultant bioavailability. The salts necessarily introduce counterions, which although physiologically tolerable, nonetheless represent needless masses of therapeutically irrelevant material that are administered to a patient.

[0006] When administered to humans, many drugs do not tolerate the harsh conditions of the stomach, where the lower pH values in the range from about 5.0 (fed) to about 1.7 (fasted) are more than adequate to induce serious chemical degradation of the drugs. Moreover, drugs generally are not absorbed in the stomach but rather in the duodenum (pH = ~4.6, fasted), jejunum (pH = ~4.5 - 5.5, fed; ~6.1 - 6.5, fasted), ileum (pH = ~6.5), and colon (pH = ~8.0) where the pH ranges typically do not facilitate decomposition of the drugs that are acid labile. The foregoing pH ranges may vary from person to person, while other ranges may pertain to other species. A more complete discussion of these pH ranges is given by A. Andeev, Absorption and Drug Development: Solubility, Permeability, and Charge State, Wiley, New York (2003). In this regard, the absence of drug degradation products typically is associated with drugs that are safer for patients. Thus, it is vitally important to ensure the safe passage of drugs through the stomach. Consequently, it is sometimes necessary to increase the dosage of a drug to compensate for the drug's decomposition in the stomach, thus ensuring that a patient receives the therapeutically effective dose of the drug. However, administering greater doses of a drug can present a number of undesirable side effects, such as, for example, irritation or damaging of the stomach lining. This damage of the gastric mucosa may be especially pronounced with the use of non-steroidal anti-inflammatory drugs (NSAIDs). Additionally, many dosage forms incorporate protective coatings and fillers to protect drugs from stomach acid. The resultant increased bulk of the dosage forms is yet another undesirable effect for the reasons mentioned above.

[0007] One highly useful subset of drug combinations is NSAIDs and narcotic analgesics (typically opioids). NSAIDs are typically thought to have a mode of action

through the arachidonic acid cascade and primarily work at the compartment of injury, resulting in a decrease in the amount of proinflammatory prostaglandins that are produced by cyclooxygenase and lipoxygenase enzymes. On the other hand, analgesics are thought to bind to various types of opioid receptors preventing painful stimuli from reaching the thalamus. It is possible that NSAIDs bind to opioid receptors and that opioid analgesics bind to cyclooxygenases and lipoxygenases, albeit weakly. Together, co-administration of NSAIDs and opioid analgesics have the potential of acting via several mechanisms to ensure the reduction of pain sensation. Additionally, the pairing of an NSAID with a narcotic can result in additive and possibly synergistic analgesic effects and thus minimize the dose of the narcotic and NSAID and their respective side effects. For other reasons as outlined above, however, it may not be necessary or desirable to administer a narcotic and NSAID at full doses to achieve the intended therapeutic effect. Employing lowered narcotic and/or NSAID doses but obtaining the full therapeutic advantages of the narcotic and NSAID would thus present a significant advance over conventional therapies.

[0008] Although the mechanism by which NSAIDs cause gastric mucosal damage is not known with certainty, two theories are postulated in the scientific and medical literature. The first model assumes that the protonated acidic NSAID is sufficiently lipophilic to penetrate the cell wall. At the pH interior to the cell, the acidic NSAID loses its proton and becomes trapped in the gastric mucosal cell, causing damage. The second model postulates that a non-selective NSAID binds both isoforms of cyclooxygenase, COX-1 and COX-2. The binding to COX-1 prevents the production of prostaglandins that are thought to repair gastric mucosal damage. Therefore, to prevent gastric mucosal damage, it is desirable to modify the chemical form of the NSAID so that it is not possible for the proton transfer reaction to occur in the stomach. An advantageous result of such modification would result in an NSAID that is insoluble in the acidic pH range of the stomach, but soluble in the neutral to basic pH range of the remainder of the alimentary canal.

[0009] In light of the foregoing shortcomings of conventional combination therapies, there exist the needs to co-administer a narcotic and NSAID as a single chemical entity, free of unnecessary counterions, that could achieve the full

therapeutic effects of the narcotic and NSAID but avoid the full narcotic dosage of conventional narcotic therapies. Accordingly, the present invention satisfies all of these needs and more by providing an NSAID and narcotic ion pair.

SUMMARY OF THE INVENTION

[0010] The present invention thus provides as one object an ion pair compound according to general formula I:

$$[\text{narcotic}]^{+}[A]^{-} \qquad (I)$$

[0011] The moiety denoted "$[\text{narcotic}]^{+}$" represents at least one cation of at least one narcotic agent or one or more stereochemical isomers thereof, while $[A]^{-}$ represents at least one anion of at least one NSAID or one or more stereochemical isomers thereof. The ion pair compound may also exist as a pharmaceutically acceptable solvate, hydrate, one or more polymorphs, or isotopically labeled version thereof.

[0012] The invention provides as another object a pharmaceutical composition comprising a therapeutically effective amount of the inventive ion pair compound and a pharmaceutically acceptable carrier, diluent, excipient, stimulant, or combination thereof. In one embodiment, the pharmaceutical composition comprises an additional NSAID, which can be the same or different as the NSAID represented by A in general formula (I).

[0013] Another object of the invention provides a method of treating a condition for which an analgesic is indicated in animals comprising administering to an animal in need of treatment a therapeutically effective amount of the instant ion pair compound. In one alternative, the condition may indicate an anti-inflammatory agent. In another alternative, the condition may indicate both an analgesic and an anti-inflammatory agent. In the foregoing methods, it is possible to employ either the present ion pair compound itself or the present pharmaceutical compositions. All of these combinations are contemplated.

[0014] It is yet another object of this invention to provide for a process of preparing the ion pair compound of general formula (I). The process comprises contacting a salt

of the formula $\{[\text{narcotic}]^+\}_x X^{-x}$ with a salt of the formula $[A]^-B^+$, wherein x is 1, 2, or 3. X is an anion with a charge of $-x$ and B^+ is a cation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 is an ORTEP of codeine diclofenate monohydrate showing selected atom labels (hydrogen atoms not shown for clarity; 40% thermal ellipsoids).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] The inventors surprisingly discovered that a wide range of narcotic agents, available in their cationic forms, combine readily with NSAIDs in their anionic forms, to yield acid insoluble or acid poorly soluble ion pair compounds of general formula (I) as summarized above. The inventive compounds thus provide a convenient source of two active agents that exhibit remarkable chemical stability to conditions under which the individual free narcotics and/or NSAIDs may decompose or potentially cause gastric mucosal damage.

Ion Pair Compounds

[0017] The narcotics that are suitable in the context of this invention are not limited in any particular manner. According to general formula (I), the narcotic should be available in a form that is amenable to the formation of a cation. Most narcotic agents meet this requirement by virtue of their bearing Brönsted acidic moieties, such as amine or amino groups, that can be ionized according to the process of this invention as described more fully below. Additionally, the invention contemplates all stereochemical isomers, where applicable, of the narcotic.

[0018] Preferred narcotics in this regard include but are not limited to ketamine, oxycodone, propoxyphene, methadone, hydrocodone, morphine, codeine, fentanyl, meperidine, hydromorphone, oxymorphone, dihydrocodeine, nalbuphine, and buprenorphine. More preferred are meperidine, ketamine, oxycodone, propoxyphene, methadone, hydrocodone, morphine, and codeine. Even more preferred are meperidine, morphine, codeine, methadone, oxycodone, and propoxyphene. The most preferred narcotic is propoxyphene.

[0019] In principle, any NSAID is appropriate for use in this invention. According to general formula (I), the NSAID is capable of forming an anion so as to provide charge neutrality for the positively charged narcotic ion. Preferred classes of NSAIDs include but are not limited to non-selective COX inhibitors, selective COX-2 inhibitors, selective COX-1 inhibitors, COX-LOX inhibitors, and PLA_2 inhibitors. The NSAID may be present as one or more stereochemical isomers, where applicable. Exemplary NSAIDs include diclofenac, etodolac, sulindac, alclofenac, fenclofenac, diflunisal, benorylate, fosfosal, salicylic acid, acetylsalicylic acid, ibuprofen, ketoprofen, naproxen, carprofen, fenbufen, flurbiprofen, oxaprozin, suprofen, triaprofenic acid, fenoprofen, indoprofen, piroprofen, flufenamic, mefenamic, meclofenamic, niflumic, salsalate, rolmerin, fentiazac, tilomisole, oxyphenbutazone, phenylbutazone, apazone, feprazone, sudoxicam, isoxicam, tenoxicam, piroxicam, indomethacin, meloxicam, nabumetone, tolmetin, lumiracoxib, and parecoxib. Preferably, the NSAID is diclofenac. In the context of this invention, NSAID is understood to exclude acetaminophen.

[0020] The invention thus contemplates all possible combinations of narcotics and NSAIDs according to general formula (I). Exemplary ion pair compounds in this regard include but are not limited to: propoxyphene naproxenate, propoxyphene etodolate, propoxyphene ketoprofenate, propoxyphene sulindate, propoxyphene suprofenate, propoxyphene flurbiprofenate, propoxyphene tolmetinate, propoxyphene fenoprofenate, propoxyphene oxaprozinate, propoxyphene difunisalate, propoxyphene loxoprofenate, ketamine ibuprofenate, ketamine acetylsalicylate, ketamine indomethacinate, ketamine naproxenate, ketamine etodolate, ketamine sulindate, ketamine ketoprofenate, ketamine suprofenate, ketamine flurbiprofenate, ketamine tolmetinate, ketamine fenoprofenate, ketamine oxaprozinate, ketamine difunisalate, ketamine loxoprofenate, ketamine salicylate, ketamine diclofenate, methadone ibuprofenate, methadone acetylsalicylate, methadone salicylate, methadone indomethacinate, methadone naproxenate, methadone etodolate, methadone sulinate, methadone ketoprofenate, methadone suprofenate, methadone flurbiprofenate, methadone tolmetinate, methadone fenoprofenate, methadone oxaprozinate, methadone difunisalate, methadone loxoprofenate, hydrocodone ibuprofenate,

hydrocodone acetylsalicylate, hydrocodone salicylate, hydrocodone indomethacinate, hydrocodone naproxenate, hydrocodone etodolate, hydrocodone sulindate, hydrocodone ketoprofenate, hydrocodone suprofenate, hydrocodone flurbiprofenate, hydrocodone tolmetinate, hydrocodone fenoprofenate, hydrocodone oxaprozinate, hydrocodone difunisalate, hydrocodone loxoprofenate, codeine ibuprofenate, codeine acetylsalicylate, codeine salicylate, codeine indomethacinate, codeine naproxenate, codeine etodolate, codeine sulindate, codeine ketoprofenate, codeine suprofenate, codeine flurbiprofenate, codeine tolmetinate, codeine fenoprofenate, codeine oxaprozinate, codeine difunisalate, codeine loxoprofenate, morphine ibuprofenate, morphine acetylsalicylate, morphine salicylate, morphine indomethacinate, morphine naproxenate, morphine etodolate, morphine sulindate, morphine ketoprofenate, morphine suprofenate, morphine flurbiprofenate, morphine tolmetinate, morphine fenoprofenate, morphine oxaprozinate, morphine difunisalate, morphine loxoprofenate, levorphanol ibuprofenate, levorphanol acetylsalicylate, levorphanol salicylate, levorphanol indomethacinate, levorphanol naproxenate, levorphanol etodolate, levorphanol sulindate, levorphanol ketoprofenate, levorphanol suprofenate, levorphanol flurbiprofenate, levorphanol tolmetinate, levorphanol fenoprofenate, levorphanol oxaprozinate, levorphanol difunisalate, levorphanol loxoprofenate, oxycodone ibuprofenate, oxycodone acetylsalicylate, oxycodone salicylate, oxycodone indomethacinate, oxycodone naproxenate, oxycodone etodolate, oxycodone sulindate, oxycodone ketoprofenate, oxycodone suprofenate, oxycodone flurbiprofenate, oxycodone tolmetinate, oxycodone fenoprofenate, oxycodone oxaprozinate, oxycodone difunisalate, oxycodone loxoprofenate; fentanyl naproxenate, fentanyl etodolate, fentanyl ketoprofenate, fentanyl sulindate, fentanyl suprofenate, fentanyl flurbiprofenate, fentanyl tolmetinate, fentanyl fenoprofenate, fentanyl oxaprozinate, fentanyl difunisalate, fentanyl loxoprofenate, meperidine naproxenate, meperidine etodolate, meperidine ketoprofenate, meperidine sulindate, meperidine suprofenate, meperidine flurbiprofenate, meperidine tolmetinate, meperidine fenoprofenate, meperidine oxaprozinate, meperidine difunisalate, meperidine loxoprofenate, hydromorphone naproxenate, hydromorphone etodolate, hydromorphone ketoprofenate, hydromorphone sulindate, hydromorphone

suprofenate, hydromorphone flurbiprofenate, hydromorphone tolmetinate, hydromorphone fenoprofenate, hydromorphone oxaprozinate, hydromorphone difunisalate, hydromorphone loxoprofenate, oxymorphone naproxenate, oxymorphone etodolate, oxymorphone ketoprofenate, oxymorphone sulindate, oxymorphone suprofenate, oxymorphone flurbiprofenate, oxymorphone tolmetinate, oxymorphone fenoprofenate, oxymorphone oxaprozinate, oxymorphone difunisalate, oxymorphone loxoprofenate, dihydrocodeine naproxenate, dihydrocodeine etodolate, dihydrocodeine ketoprofenate, dihydrocodeine sulindate, dihydrocodeine suprofenate, dihydrocodeine flurbiprofenate, dihydrocodeine tolmetinate, dihydrocodeine fenoprofenate, dihydrocodeine oxaprozinate, dihydrocodeine difunisalate, and dihydrocodeine loxoprofenate.

[0021] Preferred embodiments of the ion pair compound include propoxyphene diclofenate, ketamine diclofenate, methadone diclofenate, hydrocodone diclofenate, codeine diclofenate, propoxyphene salicylate, propoxyphene acetylsalicylate, propoxyphene ibuprofenate, morphine diclofenate, and oxycodone diclofenate. More preferably, the ion pair compound is selected from propoxyphene diclofenate, ketamine diclofenate, methadone diclofenate, hydrocodone diclofenate, codeine diclofenate, morphine diclofenate, and oxycodone diclofenate. The most preferred ion pair compound is propoxyphene diclofenate. In other embodiments, the ion pair compound is propoxyphene salicylate, propoxyphene acetylsalicylate, and propoxyphene ibuprofenate.

[0022] In other embodiments, the ion pair compound preferably is propoxyphene lumiracoxibate, ketamine lumiracoxibate, methadone lumiracoxibate, hydrocodone lumiracoxibate, codeine lumiracoxibate, morphine lumiracoxibate, or oxycodone lumiracoxibate. Alternatively, the ion pair compound is selected from the group consisting of propoxyphene parecoxibate, ketamine parecoxibate, methadone parecoxibate, hydrocodone parecoxibate, codeine parecoxibate, morphine parecoxibate, and oxycodone parecoxibate.

[0023] The ion pair compound may exist as a pharmaceutically acceptable solvate, hydrate, polymorph, or isotopically labeled version. Pharmaceutically acceptable solvates are those that include, for example, *N,N*-dimethylformamide (DMF),

dimethylsulfoxide (DMSO), acetone, ethers such as diethylether, and alcohols such as methanol and ethanol.

[0024] The ion pair compound, when crystalline or micro-crystalline, may exhibit or display a preferred morphology. However, the ion pair compound may exist in one or more other crystal morphologies. Thus, a bulk sample of the compound can include one or more crystal morphologies.

[0025] The invention also contemplates isotopically labeled ion pair compounds at one or more atoms. Useful labels in this regard include but are not limited to deuterium, tritium, ^{14}C, ^{13}C, pure ^{12}C, ^{11}C, ^{17}O, ^{14}N, ^{15}N, ^{35}Cl, and ^{37}Cl.

[0026] The bulk ion pair compound thus may comprise any and all combinations of solvates, hydrates, polymorphs, and isotopically labeled versions.

[0027] The inventors were surprised to discover that, relative to an individual narcotic or NSAID, the inventive ion pair compound is decreasingly soluble at lower than neutral pH values, typically becoming completely or at least virtually insoluble at low pH values (e.g., about pH 3 and lower). By contrast, the ion pair compound typically exhibits maximum solubility at pH values of about 7 and higher.

[0028] While not wishing to be bound by any particular theory, the inventors believe that the foregoing solubility properties advantageously permit the ion pair compound to exist generally undeterred in the acidic gastric juice of a patient. Under these conditions, the ion pair compound does not solubilize, and thus essentially protects a patient against the risk of the narcotic and/or NSAID decomposing in the stomach, and thereby frequently allows lower dosing. Additionally, the insolubility at low pH avoids, or in the least, minimizes, the potential for gastrointestinal toxicity, such as that of the NSAID irritating or inflaming the stomach lining that is typically observed with NSAIDs generally exhibiting solubility in the acidic stomach environment. Once the ion pair compound passes into the small intestine, where the pH is greater (i.e., about 7), the ion pair compound solubilizes to render the narcotic and NSAID agents as bioavailable therapeutic agents. Thus, the ion pair compound conveniently affords the narcotic and NSAID in one chemical entity that withstands the harsh conditions of the stomach, but readily evolves the drugs in the anatomy where they can be absorbed.

[0029] The invention also contemplates a composition comprising a plurality of ion pair compounds, their pharmaceutically acceptable solvates, hydrates, polymorphs, and/or isotopically labeled versions thereof. The composition thus represents the bulk solid that conforms to general formula (I). Any of the foregoing combinations are included in the invention. For example, the composition provides for ion pair compounds that have different narcotic agents and/or NSAIDs. Preferably, however, the composition is homogeneous with respect to the narcotic agent and NSAID. In other embodiments, for example, the composition encompasses one or more polymorphs of the ion pair compound.

Pharmaceutical Composition

[0030] The invention also contemplates pharmaceutical compositions that comprise a therapeutically effective amount of at least one ion pair compound according to this invention and a pharmaceutically acceptable carrier, diluent, excipient, stimulant, or combination thereof, the selection of which is known to the skilled artisan. In one embodiment, a solid pharmaceutical composition of the present invention is blended with at least one pharmaceutically acceptable excipient, diluted by an excipient or enclosed within such a carrier that can be in the form of a capsule, sachet, tablet, buccal, lozenge, paper, or other container. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the ion pair compound. Thus, the formulations can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, capsules (such as, for example, soft and hard gelatin capsules), suppositories, lozenges, buccal dosage forms, sterile injectable solutions, and sterile packaged powders.

[0031] Examples of suitable excipients include, but are not limited to, starches, gum arabic, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The compositions can additionally include lubricating agents such as, for example, talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propyl hydroxybenzoates; sweetening agents; or flavoring agents. Polyols, buffers, and inert fillers may also be used. Examples of polyols include, but are not

limited to: mannitol, sorbitol, xylitol, sucrose, maltose, glucose, lactose, dextrose, and the like. Suitable buffers encompass, but are not limited to, phosphate, citrate, tartrate, succinate, and the like. Other inert fillers which may be used encompass those which are known in the art and are useful in the manufacture of various dosage forms. If desired, the solid pharmaceutical compositions may include other components such as bulking agents and/or granulating agents, and the like. The compositions of the invention can be formulated so as to provide normal, sustained, or delayed release of the ion pair compound after administration to the patient by employing procedures well known in the art.

[0032] The pharmaceutical composition also may include one or more stimulants, Suitable stimulants in this regard include but are not limited to an effective amount of an amphetamine, such as amphetamine sulfate, dextroamphetamine sulfate, methamphetamine hydrochloride, combinations of amphetamines, derivatives and pharmaceutically salts thereof; pemoline, derivatives and pharmaceutically acceptable salts thereof; methylphenidate, derivatives and pharmaceutically acceptable salts thereof; caffeine, derivatives and pharmaceutically acceptable salts thereof; and centrally acting alpha-1 agonists such as modafinil, epinephrine, norepinephrine, phenylephrine, derivatives thereof and pharmaceutically acceptable salts thereof. The stimulant is intended to reduce or prevent possible dizziness, depression, difficulty in being mobile, drowsiness, lethargy, weakness in the extremities, and orthostatic hypotension associated with administering the ion pair compound of this invention. The preferred stimulant for the treatment of the side effects mentioned above is caffeine.

[0033] Some individuals may require a non-amphetamine based stimulant or cannot otherwise receive additional or increased amphetamine doses due to cardiovascular risk concerns. In an alternative embodiment, therefore, a centrally acting alpha-1 agonist, such as modafinil, can be used as a substitute or adjunct for an amphetamine(s), as the stimulant.

[0034] A preferred pharmaceutical composition comprises at least one dispersing agent selected from the group consisting of polymer-based dispersing agents and carbohydrate-based dispersing agents and at least one solubilizing agent. The ratio of

the ion pair compound to the polymer-based dispersing agent falls in the range from about 3:1 (w/w) to about 1:50 (w/w), while the ratio of the ion pair compound to the carbohydrate-based dispersing agent is from about 3:1 (w/w) to about 1:20 (w/w). Exemplary compositions of this type are described, for example, in U.S. Pat. Nos. 6,365,180 to Meyer et al. and 6,287,594 to Wilson et al. Such dispersing agents are well known in the art and include, for example, the polymer-based dispersing agents which include, for example, polyvinylpyrrolidone (PVP; commercially known as Plasdone.RTM.), and the carbohydrate-based dispersing agents such as, for example, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), and the cyclodextrins. Preferred dispersing agents include PVP K29-32, dextrins, starch, derivatized starch and dextrans, while of the dextrins, derivatized cyclodextrins are especially preferred. Of such cyclodextrins, hydroxypropyl .beta.-cyclodextrin and .gamma.-cyclodexrin are especially preferred. The numbers the polymer names refer to the molecular weight of the polymer wherein, for example, PVP K-30 has an average molecular weight of about 30,000, with attendant viscosity characteristics. One or more dispersing agents can be used.

[0035] Solubilizing agents suitable for use in the present context are well known in the art and are typically represented by the family of compounds known as polyethylene glycols (PEG) having molecular weights from about 200 to about 8,000. For compositions of the present invention when a liquid is desired for the final formulation or a liquid is to be used to fill soft capsules, preferably soft gelatin capsules, preferred molecular weights range from about 200 to about 600 with PEG 400 being especially preferred. For composition of the present invention when a semi-solid is preferred, especially for filling a hard capsule, preferably a hard gelatin capsule, preferred molecular weight is about 3350 while an especially preferred molecular weight is 3350 plus sufficient 400 molecular weight PEG to improve capsule filling characteristics.

[0036] Another solubilizing agent which may be utilized in compositions of the present invention is water, especially purified, and most preferably, deionized. For such compositions, the concentration of water is from about zero percent to about ninety-nine percent (w/w). More particularly for compositions of the present

invention to be filled into soft capsules, a maximum water concentration from about 0% to about 5% is preferred, although the concentration of total solubilizing agent may be the full concentration range taught herein.

[0037] As used in the present compositions, the concentration of the sum of solubilizing agent utilized, wherein more than one plasticizing agent can be utilized, is from about 0 percent (just greater than zero) to about 99 percent (w/w). The preferred concentration of solubilizing agent in the present compositions is from about 60 percent to about 90 percent (w/w).

[0038] One optional component of compositions of the present invention, but which should be used when such compositions are to be filled in soft capsules, is at least one pharmaceutically acceptable and non-toxic plasticizing agent. Such plasticizing agents, which are well known in the pharmaceutical formulation art, include, for example, glycerin, propylene glycol, and sorbitol. Such commercially available plasticizers can be prepared to include more than one plasticizing agent component, but the preferred plasticizing agent for the present compositions is glycerin. In addition to its use as a plasticizing agent, propylene glycol can be used as a solubilizing agent when used alone or in combination with another solubilizing agent as taught herein.

[0039] As used in the present invention, the concentration of the sum of plasticizing agent utilized, wherein more than one plasticizing agent can be utilized, is from about zero percent (just greater than zero) to about 75 percent (w/w). The preferred concentration of plasticizing agent is from about zero percent (0%) to about fifty percent (50%), and an especially preferred concentration in a range from about one percent (1%) to about thirty percent (30%). When the compositions of the present invention are used to fill soft capsules, the preferred concentration of such plasticizing agent is from about 5 percent to about 10 percent (w/w). Such plasticizers are especially useful with soft capsule preparations because, without which, such capsules tend to harden and lose their beneficial properties by potentially cracking or becoming brittle.

[0040] Another optional component of the present compositions, which is a preferred component, is at least one pharmaceutically acceptable, non-toxic,

surfactant, preferably a non-ionic surfactant. Such surfactants are well known in the pharmaceutical formulation art and include readily available surfactants having a concentration from about zero percent to about 90 percent such as, for example, macro gel esters (Labrafils), Tandem 522.RTM., Span 80.RTM., Gelucieres.RTM. such as, for example, tocopherol polyethylene glycol 1000 succinate, polysorbate 20, and polysorbate 80. Of these, polysorbate 20 and polysorbate 80 are preferred

[0041] As used in the present invention, the concentration of the sum of non-ionic surfactant utilized, wherein more than one such surfactant can be utilized, is from about zero percent to about 10 percent (w/w), with a range from about 1 percent to about 5 percent (w/w) being preferred. An especially preferred concentration is about 3 percent (w/w).

[0042] In the event that the foregoing compositions are to be used for parenteral administration, such a formulation typically comprises sterile aqueous and non-aqueous injection solutions comprising the ion pair compound, for which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents.

[0043] The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampules and vials. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0044] In preferred embodiments of the invention, the composition may be made into the form of dosage units for oral administration. The ion pair compound may be mixed with a solid, pulverant carrier such as, for example, lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an antifriction agent such as, for example, magnesium stearate, calcium stearate, and polyethylene glycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating, various

dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.

[0045] Soft capsules also may be prepared in which capsules contain a mixture of the ion pair compound and vegetable oil or non-aqueous, water miscible materials such as, for example, polyethylene glycol and the like. Hard capsules may contain granules of the ion pair compound in combination with a solid, pulverulent carrier, such as, for example, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

[0046] Dosage units for rectal administration may be prepared in the form of suppositories which may contain the ion pair compound in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

[0047] Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g., solutions containing an ion pair compound, sugar, and a mixture of ethanol, water, glycerol, and propylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, and saccharin. Thickening agents such as carboxymethylcellulose may also be used.

[0048] Tablets for oral use are typically prepared in the following manner, although other techniques may be employed. The solid substances are gently ground or sieved to a desired particle size, and the binding agent is homogenized and suspended in a suitable solvent. The ion pair compound and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension. The moistening typically causes the particles to aggregate slightly, and the resulting mass is gently pressed through a stainless steel sieve having a desired size. The layers of the mixture are then dried in controlled drying units for determined length of time to achieve a desired particle size and consistency. The granules of the dried mixture are gently sieved to remove any powder. To this mixture, disintegrating, anti-friction, and anti-adhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The operating parameters of the machine may be selected by the skilled artisan.

[0049] Typically, preparation of lozenge and buccal dosage forms are prepared by methods known to one of ordinary skill in the art.

[0050] In other embodiments, the ion pair compound may be present in a core surrounded by one or more layers including, for example, an enteric coating layer with or without a protective sub-coating as known to the ordinarily skilled artisan relative to pharmaceutical formulations.

[0051] The final dosage form encompassing the above embodiments may be either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard capsules or sachets or pellets formulated into tablets. It is desirable for long term stability during storage that the water content of the final dosage form containing the ion pair compound (enteric coated tablets, capsules or pellets) be kept low. As a consequence, the final package containing hard capsules filled with enteric coated pellets preferably also contain a desiccant, which reduces the water content of the capsule shell to a level where the water content of the enteric coated pellets filled in the capsules does not exceed a certain level.

[0052] Accordingly, the ion pair compounds and compositions of the present invention are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 200 mg, and more preferably the amount set forth herein. The term "unit dosage form" refers to physically discrete units, such as capsules or tablets suitable as unitary dosages for human patients and other mammals, each unit containing a predetermined quantity of one or more ion pair compound(s) calculated to produce the desired therapeutic effect, in association with at least one pharmaceutically acceptable carrier, diluent, excipient, or combination thereof. Generally, preferred dosages of the ion pair compounds in such unit dosage forms are from about 5 mg to about 15 mg, about 20 mg to about 30 mg, about 40 mg to about 60 mg, and about 65 mg to about 120 mg, especially 12 mg, 25 mg, and 48 mg, and 95 mg per dosage unit.

Additional NSAID or Narcotic

[0053] As mentioned above, an advantage of the inventive ion pair compound is the ability to dose a narcotic and NSAID in one chemical entity to a patient. However, in

some circumstances, the stoichiometry between the narcotic and NSAID (e.g., 1:1) may not accommodate the prescribed overall dosage of the NSAID. Therefore, certain embodiments of the pharmaceutical composition comprise a therapetucially effective amount of an additional NSAID, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or isotopically labeled version thereof. In these embodiments, the additional NSAID may be the same or different from the NSAID represented by "A" in general formula (I).

[0054] Alternatively, some relative dosage requirements for a given NSAID and narcotic warrant adding to the pharmaceutical composition an additional and therapeutically effective amount of a narcotic or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or isotopically labeled version thereof. In this regard, the narcotic need not be the same as the narcotic represented by general formula (I). Preferably, however, the additional narcotic is the same as the narcotic in general formula (I).

[0055] A preferred composition in this context comprises propoxyphene diclofenate. In this embodiment, the additional NSAID may be present as diclofenac free acid or a pharmaceutically acceptable salt thereof. Exemplary salts in this regard include the sodium and potassium salts of diclofenac.

[0056] In preferred embodiments, the additional NSAID or narcotic may be contained in an external or enteric coating as described above. The additional NSAID or narcotic thus is available for immediate, slow, delayed, sustained, pseudo-first order, pseudo-zero order, timed, controlled release, or combinations thereof. The additional NSAID or narcotic agent can be applied to the surface of a dosage form according to common methods that are known to those of ordinary skill such as applying to its surface solids in solution or suspension through the use of a sprayer that spreads them uniformly over the core or by employing nucleated compression or other suitable methods known to those of ordinary skill in the art. The external coat can comprise poly(vinyl pyrrolidone) (PVP) and poly(ethylene glycol) (PEG) and can further comprise materials such as, by way of example and without limitation, hydroxypropyl methylcellulose (HPMC), ethylcellulose (EC), hydroxyethylcellulose (HEC), sodium carboxymethyl-cellulose (CMC), dimethylaminoethyl methacrylate-

methacrylic acid ester copolymer, ethylacrylate-methylmethacrylate copolymer (GA-MMA), C-5 or 60 SH-50 (Shin-Etsu Chemical Corp.) and combinations thereof. The external coat can also comprise dissolution aids, stability modifiers, and bioabsorption enhancers.

[0057] The amount of the additional NSAID or narcotic depends upon the individual NSAID or narcotic and its dosage requirements that are known to the person of skill in the art.

Methods of Treatment

[0058] The invention also provides methods of treating a condition in an animal in need of treatment comprising administering to the animal a therapeutically effective amount of the ion pair compound or a pharmaceutical composition as described above. In some embodiments, the condition is one for which is indicated an analgesic. In other embodiments, an anti-inflammatory agent is indicated. In still other embodiments, the condition indicates both an analgesic and anti-inflammatory agent.

[0059] Preferably, the animal suffering from the condition is a mammal. More preferably, the mammal is a human being.

[0060] As used herein, the term "treatment" or "treating" contemplates partial or complete inhibition of the stated condition or disease state when an ion pair compound or its pharmaceutical composition is administered prophylactically or following the onset of the condition for which the compound or composition is administered. For the purposes of this invention, the term "prophylaxis" refers to the administration of the ion pair compound to an animal to protect the animal from any of the conditions set forth herein.

[0061] The inventive ion pair compound may treat a number of conditions including arthritic disorders, gastrointestinal conditions, inflammatory conditions, pulmonary inflammation, opthalmic diseases, central nervous systems disorders, pain, fever, inflammation-related cardiovascular disorders, angiogenesis-related disorders, benign and malignant tumors, adenomatous polyps, fibrosis which occurs with radiation treatment, endometriosis, osteoporosis, dysmenorrhea, premature labor, asthma,

eosinophil-related disorders, pyrexia, bone resorption, nephrotoxicity, hypotension, arthrosis, joint stiffness, kidney disease, liver disease, acute mastitis, diarrhea, colonic adenomas, bronchitis, allergic neuritis, cytomegalovirus infectivity, apoptosis, HIV-induced apoptosis, lumbago, psoriasis, eczema, acne, burns, dermatitis, ultraviolet radiation damage, allergic rhinitis, respiratory distress syndrome, and endotoxin shock syndrome.

[0062] The invention is particularly effective in the treatment of arthritic disorders. These include but are not limited to rheumatoid arthritis, osteoarthritis, and acute gouty arthritis.

[0063] Other conditions against which the invention is effective include primary dysmenorrhea, anklosing spondylitis, and inflammatory disorders. Exemplary inflammatory disorders in this context include tendonitis and bursitis.

[0064] By virtue of incorporating a narcotic and NSAID, the ion pair compound is also highly effective in the treatment of many types of pain. Certain types of pain contemplated by this invention arise from pre-operative, post-operative, and both pre- and post-operative procedures. Examples of pain that are treated by this invention thus include anogenital, minor arthritic, dental, topical, associated with an upper respiratory infection, general, joint, menstrual, mild, mild to moderate, acute musculo-skeletal, moderate to moderately severe, moderate to severe, muscular, neurogenic, obstetrical, ocular, oral mucosal and gingival, post operative, pre-operative, pre- and post-operative, severe, short term, urinary tract, and pain associated with gastric hyperacidity.

[0065] Typical doses of the ion pair compound will depend upon various factors such as, for example, the individual requirement of each patient, the route of administration, and the disease. One advantage of the ion pair compound in this regard is that the dosage strength of the compound may closely match the dosages of the individual narcotic and NSAID, which are well-known to the person of skill in the art. An attending physician may adjust the dosage rate based on these and other criteria if he or she so desires. As an example, a suitable oral dosage form may encompass from about 5 to about 1000 mg total daily dose, typically administered in one single dose or equally divided doses. A more preferred range is from about 15

mg to about 600 mg total daily dose, and a most preferred range is from about 30 mg to about 300 mg total daily dose. Additionally, the ion pair compound(s) may be administered as a suspension, and, as an example, the daily doses set forth above may be employed. In one embodiment, the ion pair compound(s) may be added in appropriate amounts to a liquid such that the resultant suspension comprises, for example, from about 0.1 mg/mL to about 10 mg/mL of the ion pair compound(s). It should be noted that daily doses other than those described above may be administered to a subject, as appreciated by an attending physician.

Process for Preparing

[0066] The invention also provides a process for preparing the ion pair compound represented by general formula (I). In general, as described summarily above, the narcotic is introduced as a cation according to the formula $\{[\text{narcotic}]^{+}\}_x X^{x-}$. In this regard, x is 1, 2, or 3, while X is a charge-balancing anion with an overall charge of $-x$. Anions represented by X include but are not limited to halides, such as chloride, bromide, and iodide; sulfate; nitrate; and phosphate. X may also represent one of many organic anions, such as carboxylates and organic sulfates or sulfonates. Exemplary anions in this regard include napsylate, terephthalate, citrate, bitartrate, and tartrate. Additional anions include the conjugate bases of the acids that are described below. It is thus possible to employ narcotic starting materials that incorporate multiple narcotic cations. Many narcotics are available commercially as salts represented by $\{[\text{narcotic}]^{+}\}_x X^{x-}$. Typically, x is 1. Examples in this regard include hydrohalogen acid salts, such as hydrochloride salts.

[0067] Where the narcotic is not available as a salt, acid addition salts of the narcotic may be prepared straightforwardly. Acids suitable for making such salts include but are not limited to hydrohalogen acids, sulfuric, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic, heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic,

halogenbenzenesulfonic, toluenesulfonic, naphtylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.

[0068] The narcotic salt of the formula $\{[narcotic]^+\}_xX^{x-}$ is contacted with an NSAID salt of the formula $[A]^-[B]^+$, where B represents the charge balancing cation for the negatively charged NSAID. Many NSAIDs already are available commercially as salts of this formula. For example, a preferred salt in this regard is sodium diclofenac. Salts of the formula $[A]^-[B]^+$ can be prepared where an NSAID is not readily available as a salt. Such salts typically are prepared from an NSAID that bears at least one "acidic" proton. The proton may be removed, for example, by a type of base that allows for the formation of an anionic species of the NSAID countered by the cation. Some embodiments encompass polar, protic environments, in which alkali or alkaline metal hydroxide or alkaline metal alkoxides present are effective in an alcohol or in mixed organic solvent such as a 2-butanone-toluene mixture.

[0069] The narcotic and NSAID salts, as set forth above, may be combined in a variety of ways to yield the present ion pair compound. In one embodiment, the compounds of formulae $\{[narcotic]^+\}_xX^{x-}$ and $[A]^-[B]^+$ thus are dissolved in separate volumes of the same solvent or in different solvents. When combined, the resultant solution thus yields the ion pair compound of general formula (I) and the stoichiometric amounts of the undesired counterions X^{x-} and B^+. The solvent or solvent mixture can be selected such that the ion pair compound precipitates when the separate volumes of $\{[narcotic]^+\}_xX^{x-}$ and $[A]^-[B]^+$ are combined, thereby allowing the easy isolation of the ion pair compound. Alternatively, the ion pair compound is soluble in the combined volumes of solvent or different solvents. In this scenario, the solvent(s) may be removed to yield the ion pair compound, which can then be purified according to standard purification techniques known to those who are skilled in the art.

[0070] In another embodiment, the compounds according to formulae $\{[narcotic]^+\}_xX^{x-}$ and $[A]^-[B]^+$ are contacted effectively with each other on a cation exchange medium, such as on a cation exchange chromatography column. In this embodiment, the $[narcotic]^+$ is retained on the cation exchange column when

$\{[\text{narcotic}]^+\}_x X^{x-}$ is introduced. When $[A]^-[B]^+$ is passed through the cation exchange column, the $[B]^+$ is retained and the desired $[\text{narcotic}]^+[A]^-$ ion pair compound is recovered and subsequently isolated according to conventional techniques in the art.

* * * * *

[0071] The following examples are intended to further describe the invention by way of illustration, and thus should not be construed as limiting the scope of the invention in any way.

[0072] All publicly available documents cited in this description are incorporated by reference as if fully set forth herein.

[0073] Example 1. Preparation of *d*-Propoxyphene Diclofenate from Sodium Diclofenac and *d*-Propoxyphene Napsylate Hydrate

[0074] Sodium {2-[(2,6-dichlorophenyl)amino]}phenylacetate (referred to herein as sodium diclofenac) (0.3283 g, 1.032 mmol) was dissolved in methanol (25 mL) to which was added a methanol solution (25 mL) of (2*S*,3*R*)-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate (referred to herein as *d*-propoxyphene) napsylate hydrate (0.5633 g, 0.996 mmol). The two solutions were mixed well and the methanol removed over several hours by evaporation under an air purge. An oily material, which contained a white residue, was formed. Water (100 mL) was added to the oily material and solution formation enhanced by means of sonication (5 minutes). The aqueous supernatant was decanted and the residual oily material dried under reduced pressure. Methanol (25 mL) was added to dissolve the oily material, and any solid material removed by filtration through 0.45-μm polytetrafluoroethylene (PTFE). Solvent was removed by evaporation under a stream of nitrogen, which resulted in the formation of an oily material. This oily material was dissolved in dichloromethane (30 mL), which resulted in the formation of a precipitate, which was removed by filtration through 0.45-μm PTFE. The dichloromethane was removed by evaporation under nitrogen to produce the desired product as an oil or glass. The product was characterized by means of Fourier Transform Infra-Red Spectroscopy (FTIR). Representative bands are listed in the Table 1.

[0075] Table 1. Observed bands for FTIR spectrum from Example 1.

Band (cm^{-1})	Intensity
3243	weak, broad
3061	weak
3032	weak
2977	moderate
2942	moderate
2819	weak
2764	weak
2819	weak
2764	weak
1733	strong
1603	moderate
1577	strong
1561	moderate
1498	strong
1453	very strong
1351	moderate
1280	moderate
1178	strong
1081	moderate
1020	moderate
773	moderate
745	moderate
704	strong

[0076] Example 2. Preparation of *d*-Propoxyphene Diclofenate from Sodium Diclofenac and *d*-Propoxyphene Napsylate Hydrate by Ion Exchange Chromatography

[0077] *d*-Propoxyphene napsylate hydrate (1.8228 g, 3.222 mmol) in methanol (60 mL) was placed on a Varian MegaBond Elut strong cation exchange column (SCX),

which was pre-treated with methanol. A solution of sodium diclofenac (1.0283 g, 3.232 mmol) in methanol (3 mL) was added to the column and the product eluted with excess methanol. The methanol solution was concentrated by rotary evaporation, reconstituted in dichloromethane (30 mL) with sufficient methanol to dissolve the material. The solution was placed in a nitrogen cabinet for approximately 12 hours. The sample was removed from the nitrogen cabinet and the remaining solvent removed by rotary evaporation, which resulted in the formation of a white solid. The solid was dissolved in methanol and placed in the nitrogen cabinet for approximately 48 hours to remove the solvent by evaporation. The resulting viscous oil containing crystalline plates was washed with acetone to dissolve the oil. The acetone solution was decanted from the insoluble crystalline plates into a small beaker. A small amount of diethyl ether was added to the acetone solution to induce recrystallization and the solution placed in a nitrogen cabinet to remove the solvent by evaporation, which resulted in the formation of an oily material. Multiple attempts at recrystallization of the oily material using different solvents and conditions did not yield a crystalline product. A small portion of the oily material from this series of attempts was dissolved in a solution of methanol and water (5:1) resulting in the formation of a white precipitate. The precipitate was separated by filtration through Whatman #4 filter paper and dried under nitrogen. The product was characterized by FTIR spectroscopy. Representative bands are listed in the Table 2.

[0078] Table 2. Observed bands for FTIR spectrum from Example 2.

Band (cm^{-1})	Intensity
3378	weak, broad
3059	weak
3031	weak
2976	weak
2923	weak
2852	weak
1734	strong
1603	moderate

Band (cm^{-1})	Intensity
1577	strong
1560	moderate
1497	strong
1454	very strong
1384	weak
1189	strong
1091	moderate
1031	moderate
972	weak
867	weak
828	weak
774	moderate
748	moderate
705	moderate
676	moderate
648	weak
624	weak
569	weak

[0079] Example 3. Preparation of *d*-Propoxyphene Diclofenate from Sodium Diclofenac and *d*-Propoxyphene Hydrochloride

[0080] Sodium diclofenac (0.9543 g, 3.000 mmol) in water (200 mL) was placed in a 500 mL Erlenmeyer flask. *d*-Propoxyphene hydrochloride (1.1219 g, 2.984 mmol) in water (200 mL) was added to the diclofenate solution resulting in the formation of a white precipitate. After mixing, the water was removed by decantation and the residual solid dissolved in an appropriate amount of diethyl ether and transferred to a 200 mL round bottom flask. The solvent was removed by rotary evaporation and the product dried under vacuum. The resulting product was a white solid.

[0081] Example 4. Preparation of *d*-Propoxyphene Diclofenate from Potassium Diclofenac and *d*-Propoxyphene Hydrochloride

[0082] Potassium diclofenac (0.3828 g, 1.145 mmol) was dissolved in water (100 mL) and placed in a 250 mL round bottom flask. An aqueous solution of *d*-propoxyphene hydrochloride (0.4384 g, 1.166 mmol in 50 mL of water) was added to the round bottom flask with stirring, which resulted in the formation of a white precipitate. The water was decanted and a small portion of the solid was analyzed by means of FTIR. Representative bands are listed in Table 3. The residual solid was dissolved in toluene (80 mL) and transferred to a separatory funnel. The organic layer was washed with water (3 × 40 mL), dried ($MgSO_4$), and the resulting solid separated by filtration through a 0.45-μm polyvinylidene fluoride (PVDF) filter. The solvent was removed by rotary evaporation, which resulted in an oily material. The product was assayed by supercritical fluid chromatography (SFC; 101.10% propoxyphene; 99.6% diclofenate).

[0083] Table 3. Observed bands for FTIR spectrum from Example 4.

Band (cm^{-1})	Intensity
3243	weak, broad
3061	weak
3031	weak
2976	moderate
2940	moderate
2818	weak
2763	weak
1733	strong
1577	moderate
1506	strong
1497	strong
1452	very strong
1350	moderate
1281	moderate

1177	strong
1080	moderate
1019	moderate
865	weak
773	moderate
746	moderate
704	strong
646	weak
579	weak
531	weak

[0084] Example 5. Preparation of *d*-Propoxyphene Diclofenate from Potassium Diclofenac and *d*-Propoxyphene Hydrochloride

[0085] Potassium diclofenac (3.3761 g, 10.101 mmol) in water (600 mL) was placed in a 1 L Erlenmeyer flask. *d*-Propoxyphene hydrochloride (3.7884 g, 10.077 mmol) in water (100 mL) was added to the diclofenate solution forming a white precipitate. After mixing for 15 minutes, the contents of the 1 L Erlenmeyer flask were transferred to a separatory funnel with the aid of a small portion of diethyl ether. Diethyl ether (250 mL) was added to the separatory funnel and any remaining precipitate was dissolved with shaking. The organic and aqueous layers were separated and the aqueous layer washed with additional diethyl ether (2 × 250 mL) to extract any remaining product. The organic layers were combined and the solvent removed by rotary evaporation. The resulting oily material was placed under reduced pressure to form a white solid. After drying to constant weight, the white solid was characterized by supercritical fluid chromatography (SFC): 100.7% propoxyphene; 98.7% diclofenac; elemental analysis (CHN): Expected: 68.03 %C, 6.34 %H, 4.41 %N, Obtained: 67.90 %C, 6.22 %H, 4.42 %N; and differential scanning calorimetry (DSC): Glass transition (T_g): 30.1 °C; degradation 189 °C).

[0086] Example 6. Preparation of *d*-Propoxyphene Diclofenate from Potassium Diclofenac and *d*-Propoxyphene Hydrochloride

[0087] Aqueous solutions of potassium diclofenac (5.0227 g, 15.027 mmol in 1 L of water) and *d*-propoxyphene hydrochloride (5.6627 g, 15.063 mmol in 300 mL of water) were combined into a 2 L round bottom flask. A white precipitate formed and the solution was stirred for 30 minutes. An appropriate amount of diethyl ether was added to the 2 L round bottom flask containing the aqueous solution and precipitate. Upon addition of the diethyl ether, the precipitate dissolved with stirring. The resulting aqueous/organic solution was transferred to a separatory funnel in several portions and the organic and aqueous layers separated. The organic layers were combined, the diethyl ether removed by rotary evaporation and the product placed under vacuum. The resulting white solid was assayed by SFC: propoxyphene 100.2%; diclofenac 99.6%.

[0088] Example 7. Preparation of *d*-Propoxyphene Diclofenate from Potassium Diclofenac and *d*-Propoxyphene Hydrochloride

[0089] Potassium diclofenac (8.3559 g, 25.000 mmol) was dissolved in water (800 mL). An aqueous solution of propoxyphene hydrochloride (9.3889 g, 24.974 mmol in 500 mL of water) was added to the diclofenac solution in a 4 L Erlenmeyer flask. A white precipitate formed and the solution was stirred for 30 minutes. An appropriate amount of diethyl ether was added to the 4 L Erlenmeyer flask containing the aqueous solution and precipitate. Upon addition of the diethyl ether, the precipitate dissolved with stirring. The resulting aqueous/organic solution was transferred to a separatory funnel in several portions and the organic and aqueous layers separated. The organic layers were combined,the diethyl ether removed by rotary evaporation and the product placed under vacuum. The resulting white solid was characterized by SFC: 98.9% propoxyphene; 99.6% diclofenac; and Nuclear Magnetic Resonance (NMR) Spectroscopy. Resonances for the ^{1}H and ^{13}C NMR spectra obtained in d_6-dimethylsulfoxide (DMSO) solution are listed in Tables 4a and 4b, respectively.

[0090] Table 4a. Observed resonances for the ^{1}H NMR spectrum from Example 7 obtained in d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons

Resonance (ppm)	Multiplicity*	Number of Protons
7.62	bs	1
7.36 - 7.50	d	2
7.38	s, d	4
7.27 - 7.34	m	1
7.15 – 7.23	m	5
7.04	t	1
6.99 - 7.01	s, d	2
6.84	t	1
6.29	dd	1
3.80	q	2
3.67	s	2
2.63	m	1
2.40	dd	1
2.27	q	2
2.06	s	6
1.60	t	1
0.94 – 1.09	t, d	6

[0091] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0092] Table 4b. Observed resonances for the ^{13}C NMR spectrum from Example 7 obtained from d_6-DMSO solution

Resonance (ppm)
173.67
172.57
142.68
139.35
137.22
136.54
130.75

Resonance (ppm)
129.96
129.80
129.13
127.81
127.47
127.21
126.82
126.38
124.55
120.64
115.89
87.62
60.75
45.31
38.59
36.43
28.32
14.31
8.99

[0093] Example 8. Preparation of *rac*-Ketamine Diclofenate from Sodium Diclofenac and *rac*-Ketamine Hydrochloride

[0094] Aqueous solutions of sodium diclofenac (0.6378 g, 2.005 mmol in 150 mL of water) and (±)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (referred to herein as *rac*-ketamine) hydrochloride (0.5427 g, 1.979 mmol in 50 mL of water) were combined into a 250 mL Erlenmeyer flask. A white precipitate formed and the solution was stirred for 15 minutes. The solid material was separated by filtration through a 0.45-μm polyvinylidene fluoride (PVDF) filter and the filter cake dissolved in methanol (25 mL). The methanol solution was removed by evaporation under nitrogen and the resulting oily material transferred to a round bottom flask using a

small amount of diethyl ether. The diethyl ether was removed by rotary evaporation forming a white solid. The flask was placed under vacuum to obtain a white solid product. The product was characterized by elemental analysis: Expected: 60.74 %C, 5.10 %H, 5.25 %N; Obtained: 59.88 %C, 4.87 %H, 5.14 %N; DSC: T_g: 40.3 °C; ^1H and ^{13}C NMR, FTIR, and FT-Raman Spectroscopy (FT-Raman). Representative bands observed in the FTIR and FT-Raman spectra are listed in the Tables 5a and 5b, respectively. Resonances for the ^1H and ^{13}C NMR spectra are listed in Tables 6a and 6b, respectively.

[0095] Table 5a. Observed bands for FTIR spectrum from Example 8.

Band (cm^{-1})	Intensity
2942	weak
1724	moderate
1578	moderate
1505	strong
1452	very strong
1375	weak
1304	moderate
1229	weak
1196	weak
1149	weak
1113	weak
1088	weak
1049	weak
947	weak
892	weak
867	weak
747	strong
715	moderate

[0096] Table 5b. Observed bands for FT-Raman spectrum from Example 8.

Band (cm^{-1})	Intensity
3070	very strong
2987	moderate
2969	moderate
2869	weak
1725	weak
1603	strong
1587	strong
1577	very strong
1448	weak
1277	weak
1250	weak
1234	moderate
1194	weak
1159	weak
1093	weak
1070	moderate
1047	strong
891	weak
837	weak
717	weak
653	weak
605	weak
517	weak
443	moderate
404	weak
363	weak
316	weak
216	weak
177	weak

[0097] Table 6a. Observed resonances for the ^{1}H NMR spectrum from Example 8 obtained from d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons
7.60	dd	1
7.52	d	2
7.26 – 7.39	m	3
7.17 – 7.22	d, t	2
7.06	t	1
6.86	t	1
6.29	dd	1
3.70	s	2
2.28 – 2.53	m	3
1.96	s	3
1.61 – 1.94	m	3

[0098] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0099] Table 6b. Observed resonances for the ^{13}C NMR spectrum from Example 8 obtained from d_6-DMSO solution.

Resonance (ppm)
204.55
173.34
142.65
139.72
137.12
132.44
130.85
130.55
129.99
129.15
128.43

Resonance (ppm)
127.46
126.76
125.51
123.98
120.73
115.94
68.63
38.29
37.94
37.85
29.33
25.01
20.43

[0100] Example 9. Preparation of *rac*-Methadone Diclofenate from Sodium Diclofenac and *rac*-Methadone Hydrochloride

[0101] Sodium diclofenac (0.6400 g, 2.012 mmol) was dissolved in water (150 mL) and placed in a 250 mL Erlenmeyer flask. A solution of (+)-6-dimethylamino-4,4-diphenyl-3-heptanone (herein referred to as *rac*-methadone) hydrochloride (0.6907 g, 1.997 mmol) in water (50 mL) was added to the diclofenate solution. A white precipitate formed and the solution was stirred for 15 minutes. After an attempt to remove the precipitate by filtration was unsuccessful, the aqueous solution and precipitate were transferred to a separatory funnel using a small portion of diethyl ether to aid in the transfer. Additional diethyl ether was added to the separatory funnel (250 mL) and any remaining precipitate was dissolved with shaking. After separation of the organic and aqueous layers, the aqueous solution was washed with additional diethyl ether (2 × 250 mL) to extract any remaining product. The organic layers were combined and the solvent removed by rotary evaporation and the product placed under reduced pressure overnight. The resulting white solid was characterized by elemental analysis: Expected: 69.42 %C, 6.33 %H, 4.63 %N; Obtained: 68.78 %C,

6.36 %H, 4.55 %N; DSC: T_g: 31.4 °C; NMR, FTIR, and FT-Raman. Representative bands observed in the FTIR and FT-Raman spectra are listed in the Tables 7a and 7b, respectively. Resonances for the ^{1}H and ^{13}C NMR spectra are listed in Tables 8a and 8b, respectively.

[0102] Table 7a. Observed bands for FTIR spectrum from Example 9.

Band (cm^{-1})	**Intensity**
3061	weak
3028	weak
2969	weak
2936	weak
1706	moderate
1587	moderate
1577	moderate
1560	weak
1497	moderate
1451	very strong
1374	weak
1305	weak
1195	weak
1150	weak
1095	weak
1046	weak
934	weak
867	weak
765	strong
747	strong
703	very strong

[0103] Table 7b. Observed bands for FT-Raman spectrum from Example 9.

Band (cm^{-1})	**Intensity**

Band (cm^{-1})	Intensity
3064	very strong
2969	moderate
2936	moderate
1705	weak
1601	strong
1577	strong
1451	weak
1274	weak
1248	weak
1236	moderate
1191	moderate
1159	moderate
1093	weak
1071	weak
1045	moderate
1035	moderate
1002	strong
838	weak
766	weak
718	weak
619	weak
605	weak
547	weak
532	weak
517	weak
444	weak
404	weak
366	weak
317	weak
289	weak

Band (cm^{-1})	Intensity
238	weak
215	weak

[0104] Table 8a. Observed resonances for the ^1H NMR spectrum from Example 9 obtained from d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons
7.88	bs	1
7.51	d	2
7.24 – 7.36	m	10
7.14 – 7.18	d, t	2
7.03	t	1
6.83	t	1
6.28	dd	1
3.64	s	2
2.91	dd	1
2.41	q	1
2.30	m	2
2.18	s	6
2.03	dd	1
0.73	t	3
0.46	d	3

[0105] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0106] Table 8b. Observed resonances for the ^{13}C NMR spectrum from Example 9 obtained from d_6-DMSO solution.

Resonance (ppm)
209.34
173.93
142.75

Resonance (ppm)
142.52
141.98
137.32
130.68
129.66
129.60
129.12
128.84
128.20
127.89
127.05
126.91
126.58
125.10
125.02
120.57
115.89
64.32
55.48
41.42
31.53
12.28
9.25

[0107] Example 10. Purity Determination of Propoxyphene Diclofenate by Supercritical Fluid Chromatography

[0108] The purity of the propoxyphene diclofenate prepared in the foregoing examples was determined by utilizing supercritical fluid chromatography ("SFC") according to the following procedure.

[0109] SFC was performed with the Analytical SFC system (Berger Instrumets, Newark, DE), utilizing a 4.6 × 250 mm cyano column (Berger instruments) maintained at 40°C. The mobile phase contained a 90:10 mixture of carbon dioxide:2.5 mM ammonium acetate in methanol. The column outlet pressure was held at 120 bar at a flow rate of 3.0 mL/minute. Standards and sample solution were prepared in methanol at about 0.5 mg/mL. Injection volume for sample and standard preparations (USP diclofenac sodium; USP propoxyphene HCl) was 10 μL and run time was less than 10 minutes. UV detection was performed at 208 nm. The chromatographic data peak areas were collected and analyzed using Millenium[32] chromatography software (Waters Corporation, Milford, MA) to generate the %w/w assay values for the samples.

[0110] Example 11. Preparation of 5R,6S,9R,13S,14R Codeine Diclofenate from Sodium Diclofenac and 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate.

[0111] Aqueous solutions of sodium diclofenac (1.2729 g, 4.001 mmol in 100 mL of water) and 7,8-didehydro-4,5*R*-epoxy-3-methoxy-9*R*,13*S*,14*R*,17-methylmorphinan-6*S*-ol (herein referred to as codeine) sulfate (1.4077 g, 2.020 mmol in 60 mL of water) were combined into a 250 mL round bottom flask. A white precipitate formed and the solution was stirred for 30 minutes. The contents of the 250 mL round bottom flask were transferred to a separatory funnel using a small portion of diethyl ether to aid in the transfer. Diethyl ether (90 mL) and chloroform (90 mL) were added to the separatory funnel and any remaining precipitate was dissolved with shaking. The organic layer was separated and the solvent removed by rotary evaporation. The resulting white solid was dissolved in diethyl ether (100 mL) and the solvent again removed by rotary evaporation. The resulting white solid was dried under reduced pressure overnight(30 °C). The product was characterized by means of DSC: T_g at 43.2 °C degradation at 182°C; and spectroscopically by NMR, FTIR, and FT-Raman. Representative bands observed in the FTIR and FT-Raman spectra are listed in Tables 9a and 9b, respectively. Resonances for the ^{1}H and ^{13}C NMR spectra are listed in Tables 10a and 10b, respectively.

[0112] Table 9a. Observed bands for FTIR spectrum from Example 11.

Band (cm^{-1})	Intensity
2936	weak
2841	weak
1634	weak
1605	weak
1587	moderate
1577	moderate
1560	weak
1504	strong
1452	very strong
1369	weak
1303	weak
1285	moderate
1274	moderate
1192	weak
1180	weak
1159	weak
1121	weak
1090	weak
1071	weak
1050	weak
1024	weak
973	weak
942	weak
930	weak
919	weak
872	weak
836	weak
749	very strong
717	moderate

Band (cm^{-1})	Intensity
696	weak
666	weak

[0113] Table 9b. Observed bands for FT-Raman spectrum from Example 11.

Band (cm^{-1})	Intensity
3069	strong
2986	very strong
2947	strong
2837	weak
1635	weak
1603	strong
1578	strong
1451	weak
1280	weak
1235	weak
1195	weak
1160	weak
1092	weak
1072	weak
1046	moderate
837	weak
715	weak
667	weak
628	weak
532	weak
443	weak
366	weak
312	weak
263	weak

[0114] Table 10a. Observed resonances for the ^{1}H NMR spectrum from Example 11 obtained from d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons
7.62	bs	1
7.51	d	2
7.15 – 7.20	d, t	2
7.05	t	1
6.85	t	1
6.63	d	1
4.48	d	1
6.28	dd	1
5.55	m	1
5.25	m	1
4.69	dd	1
4.11	m	1
3.72	s	3
3.67	s	2
3.41	m	1
2.97	d	1
2.57 – 2.65	t, dd	2
2.40	s	3
2.30 – 2.36	m	2
2.03	m	1
1.66	dd	1

[0115] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0116] Table 10b. Observed resonances for the ^{13}C NMR spectrum from Example 11 obtained from d_6-DMSO solution.

Resonance (ppm)
173.80

147.20
142.71
141.35
137.23
133.62
130.76
129.79
129.15
127.78
127.24
126.73
125.28
124.59
120.67
118.47
115.92
113.37
91.77
79.16
66.35
58.04
56.01
45.76
42.65
42.17
38.74
34.73
20.48

[0117] An attempt to recrystallize the product was performed. A portion of the solid (9 mg) was dissolved in a test tube with several drops of acetone. Water was added

until a precipitate formed and the contents of the test tube transferred to a separatory funnel containing diethyl ether (8 mL). The solid product was dissolved in the diethyl ether, and then was extracted and the organic layer separated and set aside to evaporate. Upon evaporation of the diethyl ether, the resulting product was characterized by single crystal X-ray crystallography as codeine diclofenate monohydrate. An ORTEP representation of the product is shown in FIGURE 1. Pertinent bond distances and angles corresponding to this structure are listed below in Tables 11a and 11b, respectively. Representative bands observed in the FTIR spectrum of the crystalline product are listed in Table 11c.

[0118] Table 11a. Selected Bond Distances from Example 11 crystalline product.

Bond	Distance (Å)
Cl11-C11	1.722(3)
O1-C1	1.243(3)
N9-C10	1.388(3)
C1-C2	1.538(3)
C3-C4	1.390(3)
C4-C5	1.394(5)
C6-C7	1.374(4)
C10-C15	1.389(4)
C11-C12	1.381(4)
C13-C14	1.384(4)
O21-C21	1.367(3)
O23-C22	1.368(2)
O25-C25	1.416(3)
N32-C31	1.490(3)
C21-C37	1.385(3)
C22-C38	1.371(3)
C24-C29	1.542(3)
C26-C27	1.323(3)
C28-C29	1.539(2)
C29-C38	1.509(2)
C30-C31	1.512(3)
C34-C35	1.511(3)
C35-C36	1.398(3)
Cl15-C15	1.746(2)
O2-C1	1.260(3)
N9-C8	1.408(3)

C2-C3	1.509(4)
C3-C8	1.403(4)
C5-C6	1.372(6)
C7-C8	1.393(4)
C10-C11	1.411(3)
C12-C13	1.375(5)
C14-C15	1.376(4)
O21-C21M	1.414(3)
O23-C24	1.471(2)
N32-C32	1.486(3)
N32-C33	1.513(2)
C21-C22	1.393(2)
C24-C25	1.531(3)
C25-C26	1.501(3)
C27-C28	1.513(3)
C28-C33	1.543(3)
C29-C30	1.536(2)
C33-C34	1.543(3)
C35-C38	1.383(2)
C36-C37	1.388(3)

[0119] Table 11b. Selected Bond Angles from Example 11 crystalline product.

Bond Angle	Degree
C10-N9-C8	122.7(2)
O1-C1-C2	119.4(2)
C3-C2-C1	111.5(2)
C4-C3-C2	121.3(3)
C3-C4-C5	121.7(3)
C5-C6-C7	119.7(3)
C7-C8-C3	119.6(2)
C3-C8-N9	118.8(2)
N9-C10-C11	121.7(3)
C12-C11-C10	121.9(3)
C10-C11-Cl11	119.4(2)
C15-C14-C13	118.9(3)
C14-C15-Cl15	118.1(2)
C21-O21-C21M	117.4(2)
C32-N32-C31	110.9(2)
C31-N32-C33	111.8(2)
O21-C21-C22	116.5(2)

O23-C22-C38	113.2(1)
C38-C22-C21	120.9(2)
O23-C24-C29	107.2(1)
O25-C25-C26	110.4(2)
C26-C25-C24	111.5(2)
C26-C27-C28	118.5(2)
C27-C28-C33	114.0(2)
C38-C29-C30	112.8(2)
C30-C29-C28	109.8(1)
C30-C29-C24	111.8(1)
C31-C30-C29	111.7(2)
N32-C33-C28	106.0(1)
C28-C33-C34	114.3(2)
C38-C35-C36	116.0(12)
C36-C35-C34	125.0(2)
C21-C37-C36	121.9(2)
C22-C38-C29	109.8(1)
O1-C1-O2	124.1(2)
O2-C1-C2	116.5(2)
C4-C3-C8	117.9(3)
C8-C3-C2	120.7(2)
C6-C5-C4	119.6(3)
C6-C7-C8	121.5(3)
C7-C8-N9	121.6(3)
N9-C10-C15	122.8(2)
C15-C10-C11	115.4(2)
C12-C11-Cl11	118.8(2)
C13-C12-C11	120.1(3)
C14-C15-C10	123.7(2)
C10-C15-Cl15	118.2(2)
C22-O23-C24	107.0(1)
C32-N32-C33	113.8(2)
O21-C21-C37	126.7(2)
C37-C21-C22	116.7(2)
O23-C22-C21	125.7(2)
O23-C24-C25	110.7(2)
C25-C24-C29	111.7(2)
O25-C25-C24	113.2(2)
C27-C26-C25	119.6(2)
C27-C28-C29	108.7(1)
C29-C28-C33	107.7(2)

C38-C29-C28	105.4(1)
C38-C29-C24	100.5(1)
C28-C29-C24	116.1(2)
N32-C31-C30	111.1(2)
N32-C33-C34	112.4(2)
C35-C34-C33	114.9(2)
C38-C35-C34	118.5(2)
C37-C36-C35	121.1(2)
C22-C38-C35	122.8(2)
C35-C38-C29	126.6(2)

[0120] Table 11c. Observed bands for FTIR spectrum from Example 11 crystalline product.

Band (cm^{-1})	**Intensity**
3282	moderate, broad
3221	moderate, broad
3072	moderate
3038	moderate
3013	moderate
2969	moderate
2945	moderate
2923	moderate
2834	weak
2778	weak
1631	moderate
1602	moderate
1586	moderate
1575	moderate
1560	moderate
1501	strong
1466	moderate
1448	strong

Band (cm^{-1})	Intensity
1369	moderate
1307	strong
1272	strong
1212	moderate
1190	moderate
1176	moderate
1161	moderate
1151	moderate
1122	strong
1097	strong
1044	strong
1019	moderate
982	weak
968	moderate
943	moderate
931	moderate
917	weak
883	weak
866	moderate
840	moderate
791	moderate
771	strong
753	very strong
717	weak
696	weak
676	weak

[0121] Example 12. Preparation of Propoxyphene Salicylate from Propoxyphene Hydrochloride and Sodium Salicylate.

[0122] *d*-Propoxyphene hydrochloride (1.5020 g, 4.00 mmol) in water (50 mL) was placed in a 250 mL beaker. Sodium salicylate (0.6399 g, 4.00 mmol) in water (50 mL) was added to the propoxyphene solution forming a white precipitate. After mixing for 2 hours, the contents of the beaker were transferred to a separatory funnel with the aid of a small portion of diethyl ether. Additional diethyl ether was added to the separatory funnel (100 mL) and any remaining precipitate dissolved with shaking. The aqueous and organic layers were separated and the aqueous layer was washed with an additional portion of diethyl ether (100 mL) to extract any remaining product. The organic and aqueous layers were separated again, the organic layers combined, washed with water (50 mL), and the solvent removed by rotary evaporation. The resulting oily material was placed under reduced pressure to form a white solid. After drying to constant weight, the white solid was characterized by elemental analysis: Expected: 72.93 %C, 7.39 %H, 2.98 %N; Obtained: 72.32 %C, 7.38 %H, 2.94 %N; NMR, and FTIR. Representative bands are listed in Table 12a. Resonances for the ^{1}H and ^{13}C NMR are listed in Tables 12b and 12c, respectively.

[0123] Table 12a. Observed bands for FTIR spectrum from Example 12.

Band (cm^{-1})	**Intensity**
2974	weak
1736	moderate
1631	moderate
1594	moderate
1486	strong
1456	strong
1380	strong
1346	moderate
1323	moderate
1304	moderate
1259	moderate
1175	strong
1140	moderate

Band (cm^{-1})	Intensity
1081	moderate
1027	moderate
971	weak
916	weak
891	weak
858	moderate
807	moderate
761	strong
726	moderate
704	very strong
666	moderate

[0124] Table 12b. Observed resonances for the ^1H NMR spectrum from Example 12 obtained from d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons
7.70	dd	1
7.69 – 7.71	s, d	3
7.32 – 7.40	m	1
7.20 – 7.25	m	5
7.02 – 7.04	s, d	2
6.66 – 6.72	m	2
3.82	q	2
3.23	d	1
2.70	m	1
2.57	s	6
2.25 – 2.40	m	3
1.05	d	3
0.97	t	3

[0125] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0126] Table 12c. Observed resonances for the ^{13}C NMR spectrum from Example 12 obtained from d_6-DMSO solution.

Resonance (ppm)
172.69
172.16
162.17
138.91
136.02
132.28
130.02
128.00
127.77
127.14
126.61
126.20
118.74
116.75
116.00
86.64
59.36
43.36
38.05
35.42
28.05
14.22
8.82

[0127] Example 13. Preparation of *d*-Propoxyphene Ibuprofenate from *d*-Propoxyphene Hydrochloride and *rac*-Ibuprofen.

[0128] A solution of (±)-2-(4-Isobutylphenyl)propionic acid (herein referred to as *rac*-ibuprofen) (0.3071 g, 1.49 mmol) in ethanol (20 mL) was placed in a 50 mL beaker. Potassium hydroxide (0.083512 g, 1.49 mmol) in ethanol (5 mL) was added to the ibuprofen solution and stirred for 1 hour. The solvent was removed by rotary evaporation and the product dissolved in water (100 mL). Propoxyphene hydrochloride (0.5611 g, 1.49 mmol) in water (100 mL) was placed in a 500 mL beaker. The aqueous ibuprofen solution was added to the propoxyphene solution forming a white precipitate. After mixing for 1.5 hours, the contents of the 500 mL beakerwere transferred to a separatory funnel with the aid of a small portion of diethyl ether. Additional diethyl ether was added to the separatory funnel (125 mL) and any remaining precipitate was dissolved with shaking. The aqueous and organic layers were separated and the aqueous layer washed with additional portions of diethyl ether (2 × 125 mL) to extract any remaining product. The organic layers were combined, washed with water (2 × 100 mL), and the solvent removed by rotary evaporation. The resulting oily material was placed under reduced pressure. After drying to constant weight, the oily material was characterized by elemental analysis: Expected: 77.03 %C, 8.68 %H, 2.57 %N; Obtained: 77.11 %C, 8.63 %H, 2.55 %N; NMR, and FTIR. Representative bands are listed in Table 13a. Resonances for the ^{1}H and ^{13}C NMR spectra are listed in Tables 13b and 13c, respectively.

[0129] Table 13a. Observed bands for FTIR spectrum from Example 13.

Band (cm^{-1})	Intensity
2955	moderate, broad
2872	weak
1731	strong
1601	weak
1499	weak
1459	moderate
1384	weak
1223	strong
1083	weak

Band (cm^{-1})	Intensity
1079	weak
1025	moderate
964	moderate, broad
707	weak

[0130] Table 13b. Observed resonances for the ^{1}H NMR spectrum from Example 13 obtained from d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons
7.34 - 7.37	m	4
7.27 – 7.29	m	1
7.16 - 7.23	m	5
7.09	d	2
7.02	dd	2
3.81	q	2
3.62	q	1
2.63	m	1
2.41	d	2
2.23 – 2.28	m	3
1.98	s	6
1.80	m	1
1.49	t	1
1.35	d	3
0.92 – 0.99	t, d	6
0.85	d	6

[0131] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0132] Table 13c. Observed resonances for the ^{13}C NMR spectrum from Example 13 obtained from d_6-DMSO solution.

Resonance (ppm)

Resonance (ppm)
175.48
172.57
139.47
138.54
136.65
129.96
128.90
127.79
127.43
127.07
126.78
126.44
126.32
87.79
61.04
45.72
44.33
44.21
38.70
36.63
29.59
28.37
22.16
18.53
14.35
9.04

[0133] Example 14. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Diclofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Sodium Diclofenac.

[0134] An aqueous solution (20 mL) of 7,8-didehydro-4,5*R*-epoxy-9*R*,13*S*,14*R*,17-methylmorphinan-3,6*S*-diol (referred to herein as morphine) sulfate pentahydrate (0.1508 g, 0.199 mmol) in water (20 mL) was placed in a 100 mL round bottom flask. Sodium diclofenac (0.1227 g, 0.386 mmol) in water (20 mL) was added to the morphine solution forming a white precipitate. After mixing for 1 hour, the precipitate was removed by filtration through a 0.45 μm polyvinylidene fluoride (PVDF) filter. The filtrate was transferred to a 50 mL round bottom flask with a small amount of acetonitrile and the solvent removed by rotary evaporation. The precipitate was dried under reduced pressure at 44 °C. The white solid was characterized by FTIR with representative bands listed in Table 14a. Resonances for the ^{1}H and ^{13}C NMR spectra are listed in Tables 14b and 14c, respectively

[0135] Table 14a. Observed bands for FTIR spectrum from Example 14.

Band (cm^{-1})	**Intensity**
3034	weak
2936	weak
1636	weak
1603	moderate
1577	moderate
1557	moderate
1503	strong
1453	very strong
1373	moderate
1313	moderate
1277	moderate
1248	moderate
1192	weak
1176	moderate
1159	moderate
1123	moderate
1070	weak

Band (cm^{-1})	Intensity
1021	weak
961	weak
944	weak
871	weak
836	weak
782	strong
747	strong
714	moderate

[0136] Table 14b. Observed resonances for the ^1H NMR spectrum from Example 14 obtained from d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons
7.68	bs	1
7.51	d	2
7.15 – 7.20	d, t	2
7.05	t	1
6.85	t	1
6.46	d	1
6.36	d	1
6.29	dd	1
5.55	d	1
5.24	m	1
4.67	dd	1
4.09	m	1
3.66	s	2
3.40	m	1
2.93	d	1
2.58 – 2.63	d, dd	2
2.40	s	3
2.27 – 2.39	dd, dd	2

Resonance (ppm)	Multiplicity*	Number of Protons
1.99 – 2.06	m	1
1.65	dd	1

[0137] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0138] Table 14c. Observed resonances for the ^{13}C NMR spectrum from Example 14 obtained from d_6-DMSO solution.

Resonance (ppm)
173.83
146.20
142.71
138.56
137.24
133.63
130.74
130.53
129.76
129.14
127.76
127.19
125.24
124.74
124.68
120.64
118.56
116.41
115.91
91.21
66.23
58.14

Resonance (ppm)
45.83
42.62
42.14
38.87
34.69
20.45

[0139] Example 15. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Diclofenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Sodium Diclofenac.

[0140] An aqueous solution (20 mL) of 4,5*R*-epoxy-14*S*-hydroxy-3-methoxy-9*R*,13*R*,17-methylmorphinan-6-one (herein referred to as oxycodone) hydrochloride (0.3433 g, 0.976 mmol) in water (20 mL) was placed in a 100 mL round bottom flask. Sodium diclofenac (0.3125 g, 0.982 mmol) in water (20 mL) was added to the oxycodone solution forming a white precipitate. After mixing for 1 hour, the aqueous solution and precipitate were transferred to a separatory funnel and diethyl ether was added (20 mL). Diethyl ether (20 mL) was also added to the 100 mL round bottom flask to dissolve any remaining precipitate. This solution was added to the separatory funnel, and any precipitate in the separatory funnel was dissolved with shaking. the organic layer separated and the solvent removed by rotary evaporation. The resulting oily material was placed under reduced pressure to form a white solid. The white solid was characterized by elemental analysis: Expected: 62.85 %C, 5.27 %H, 4.58 %N; Obtained: 62.44 %C, 5.37 %H, 4.41 %N; NMR, and FTIR. The representative bands listed in Table 15a. Resonances for the ^{1}H and ^{13}C NMR spectra are listed in Tables 15b and 15c, respectively.

[0141] Table 15a. Observed bands for FTIR spectrum from Example 15.

Band (cm^{-1})	Intensity
2932	weak
2836	weak
1727	moderate

Band (cm^{-1})	Intensity
1605	weak
1578	moderate
1505	strong
1451	very strong
1383	moderate
1279	strong
1231	weak
1163	moderate
1148	moderate
1112	weak
1071	weak
1036	moderate
986	weak
944	moderate
906	weak
881	weak
848	weak
772	strong
746	strong
713	weak

[0142] Table 15b. Observed resonances for the ^1H NMR spectrum from Example 15 obtained from d_6-DMSO solution.

Resonance (ppm)	Multiplicity*	Number of Protons
7.54	bs	1
7.51	d	2
7.15 – 7.21	d, t	2
7.05	t	1
6.85	t	1
6.76	d	1

Resonance (ppm)	Multiplicity*	Number of Protons
6.68	d	1
6.29	dd	1
4.84	s	1
3.79	s	3
3.68	s	2
3.14	d	1
2.87 – 2.97	d, m	2
2.56	dd	1
2.37 – 2.45	dd, s	4
2.01 – 2.11	m, dd	2
1.75 – 1.80	m	1
1.45	m	1
1.31	dd	1

[0143] * s – singlet, d – doublet, dd – doublet of doublets, m – multiplet, b – broad, t – triplet, q – quartet.

[0144] Table 15c. Observed resonances for the ^{13}C NMR spectrum from Example 15 obtained from d_6-DMSO solution.

Resonance (ppm)
208.35
173.60
144.41
142.68
142.03
137.19
130.79
129.86
129.42
129.14
127.28

Resonance (ppm)
125.34
125.30
124.39
120.66
119.33
115.90
114.79
89.71
69.82
63.80
56.32
49.42
45.14
38.45
35.58
31.14
29.52
21.66

[0145] Example 16. Preparation of *d*-Propoxyphene Acetylsalicylate from *d*-Propoxyphene Hydrochloride and Acetylsalicylic Acid.

[0146] Acetylsalicylic acid (0.5459 g, 3.03 mmol) in ethanol (60 mL) was placed in a 100 mL beaker. Potassium hydroxide (0.1694 g, 3.02 mmol) in ethanol (40 mL) was added to the acetylsalicylic acid solution and stirred for 1 hour. *d*-Propoxyphene hydrochloride (1.1278 g, 3.00 mmol) in water (80 mL) was placed in a 250 mL beaker. The ethanolic acetylsalicylate solution was added to the propoxyphene solution. The solution was transferred to a 500 mL round bottom flask and the volume reduced to 60 mL by rotary evaporation. After reduction, a white precipitate was observed. The contents of the 500 mL round bottom flask were transferred to a separatory funnel with the aid of a small amount of diethyl ether. Additional diethyl

ether (90 mL) was added to the separatory funnel and any remaining precipitate was dissolved with shaking. The aqueous and organic layers were separated and the aqueous layer was washed with additional diethyl ether (3 × 90 mL) to extract any remaining product. The organic layers were combined and the solvent removed by rotary evaporation forming a viscous liquid. The viscous liquid was characterized by elemental analysis: Expected: 70.94 %C, 7.94 %H, 2.51 %N; Obtained: 70.22 %C, 7.16 %H, 2.44 %N (corrected for residual solvent content); TGA: 5.4% weight loss up to 160 °C and DSC: degradation >170 °C.

[0147] Example 17. Preparation of *d*-Propoxyphene Indomethacinate from *d*-Propoxyphene Hydrochloride and Indomethacin.

[0148] *d*-Propoxyphene Indomethacinate may be prepared using the following synthetic scheme. A solution is prepared in a minimum volume of ethanol of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (herein referred to as indomethacin) (0.3578 g, 1.00 mmol) and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for one hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0149] Example 18. Preparation of *d*-Propoxyphene (*S*)-Naproxenate from *d*-Propoxyphene Hydrochloride and (*S*)-Naproxen Sodium.

[0150] *d*-Propoxyphene naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of (*S*)-6-methoxy-α-methyl-2-naphthaleneacetate (herein referred to as naproxen) sodium (0.2522 g, 1.00 mmol) and *d*-propoxyphene hydrochloride (0.3759 g, 1.00 mmol) are combined. The solution is stirred for 60 minutes. The resulting solution is extracted with diethyl ether (4 × 90 mL). The

organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0151] Example 19. Preparation of *d*-Propoxyphene Etodolate from *d*-Propoxyphene Hydrochloride and Etodolac.

[0152] *d*-Propoxyphene etodolate may be prepared using the following synthetic scheme. A solution of 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid (herein referred to as etodolac) (0.2874 g, 1.00 mmol) in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol (20 mL) and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0153] Example 20. Preparation of *d*-Propoxyphene (S)-Ketoprofenate from *d*-Propoxyphene Hydrochloride and (S)-Ketoprofen.

[0154] *d*-Propoxyphene (*S*)-ketoprofenate may be prepared using the following synthetic scheme. A solution of *(S)*-2-(3-benzoylphenyl)propionic acid (herein referred to as ketoprofen) (0.2543 g, 1.00 mmol) prepared in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0155] Example 21. Preparation of *d*-Propoxyphene Sulindate from *d*-Propoxyphene Hydrochloride and Sulindac.

[0156] *d*-Propoxyphene sulindate may be prepared using the following synthetic scheme. A solution of (*Z*)-5-Fluoro-2-methyl-1-[*p*-(methylsulfinyl)benzilidine]indenyl-3-acetic acid (herein referred to as sulindac) (0.3564 g, 1.00 mmol) is prepared in a minimal volume of ethanol and is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0157] Example 22. Preparation of *d*-Propoxyphene Suprofenate from *d*-Propoxyphene Hydrochloride and Suprofen.

[0158] *d*-Propoxyphene suprofenate may be prepared using the following synthetic scheme. A solution of (α)-methyl-*p*-(2-thenoyl)phenylacetic acid (herein referred to as suprofen) (0.2543 g, 1.00 mmol) is prepared in a minimal volume of ethanol and is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0159] Example 23. Preparation of *d*-Propoxyphene (*S*)-Flurbiprofenate from *d*-Propoxyphene Hydrochloride and (*S*)-Flurbiprofen.

[0160] *d*-Propoxyphene (*S*)-flurbiprofenate may be prepared using the following synthetic scheme. A solution of (*S*)-2-Fluoro-α-methyl-4-biphenylacetic acid (herein referred to as flurbiprofen) (0.2443 g, 1.00 mmol) is prepared in a minimal volume of ethanol and is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0161] Example 24. Preparation of *d*-Propoxyphene Tolmetinate from *d*-Propoxyphene Hydrochloride and Tolmetin Sodium Dihydrate.

[0162] *d*-Propoxyphene tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of 1-methyl-5-(*p*-toluoyl)pyrrole-2-acetic acid (herein referred to as tolmetin) sodium dihydrate (0.3153 g, 1.00 mmol) and *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) are combined into an suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0163] Example 25. Preparation of *d*-Propoxyphene Fenoprofenate from *d*-Propoxyphene Hydrochloride and Fenoprofen Calcium Trihydrate.

[0164] *d*-Propoxyphene fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of (±)-2-(3-phenoxyphenyl)propionic acid (herein referred to as fenoprofen) calcium trihydrate (0.2884 g, 0.50 mmol) and *d*-propoxyphene hydrochloride (0.3759 g, 1.00 mmol) are combined into an suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic

layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0165] Example 26. Preparation of *d*-Propoxyphene Oxaprozinate from *d*-Propoxyphene Hydrochloride and Oxaprozin.

[0166] *d*-Propoxyphene oxaprozinate may be prepared using the following synthetic scheme. A solution of 4,5-diphenyl-2-oxazolepropionic acid (herein referred to as oxaprozin) (0.2933 g, 1.00 mmol) is prepared in a minimal volume of ethanol and is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0167] Example 27. Preparation of *d*-Propoxyphene Difunisalate from *d*-Propoxyphene Hydrochloride and Difusinal.

[0168] *d*-Propoxyphene difunisalate may be prepared using the following synthetic scheme. A solution of 5-(2,4-difluorophenyl)salicylic acid (herein referred to as difunisal) (0.2502 g, 1.00 mmol) is prepared in a minimal volume of ethanol and is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0169] Example 28. Preparation of *d*-Propoxyphene Loxoprofenate from *d*-Propoxyphene Hydrochloride and Loxoprofen.

[0170] *d*-Propoxyphene loxoprofenate may be prepared using the following synthetic scheme. A solution of α-methyl-{4-[(2-oxocyclopentyl)methyl]}phenylacetic acid (herein referred to as loxoprofen) (0.2463 g, 1.00 mmol) is prepared in a minimal volume of ethanol and is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *d*-Propoxyphene hydrochloride (0.3759 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0171] Example 29. Preparation of *rac*-Ketamine Ibuprofenate from *rac*-Ketamine Hydrochloride and Ibuprofen.

[0172] *rac*-Ketamine ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0173] Example 30. Preparation of *rac*-Ketamine Acetylsalicylate from *rac*-Ketamine Hydrochloride and Acetylsalicylic Acid.

[0174] *rac*-Ketamine acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0175] **Example 31. Preparation of *rac*-Ketamine Salicylate from *rac*-Ketamine Hydrochloride and Sodium Salicylate.**

[0176] *rac*-Ketamine salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and of *rac*-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0177] **Example 32. Preparation of *rac*-Ketamine Indomethacinate from *rac*-Ketamine Hydrochloride and Indomethacin.**

[0178] *rac*-Ketamine indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with

diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0179] Example 33. Preparation of *rac*-Ketamine Naproxenate from *rac*-Ketamine Hydrochloride and Naproxen Sodium.

[0180] *rac*-Ketamine naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of *rac*-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for approximately 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0181] Example 34. Preparation of *rac*-Ketamine Etodolate from *rac*-Ketamine Hydrochloride and Etodolac.

[0182] *rac*-Ketamine etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0183] Example 35. Preparation of *rac*-Ketamine Sulindate from *rac*-Ketamine Hydrochloride and Sulindac.

[0184] *rac*-Ketamine sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal

volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0185] Example 36. Preparation of *rac*-Ketamine (*S*)-Ketoprofenate from *rac*-Ketamine Hydrochloride and (*S*)-Ketoprofen.

[0186] *rac*-Ketamine (*S*)-ketoprofenate may be prepared using the following synthetic scheme. (*S*)-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0187] Example 37. Preparation of *rac*-Ketamine Suprofenate from *rac*-Ketamine Hydrochloride and Suprofen.

[0188] *rac*-Ketamine suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) dissolved in a minimal volume of water is combined with the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers

are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0189] Example 38. Preparation of *rac*-Ketamine (*S*)-Flurbiprofenate from *rac*-Ketamine Hydrochloride and (*S*)-Flurbiprofen.

[0190] *rac*-Ketamine (*S*)-Flurbiprofenate may be prepared using the following synthetic scheme. (*S*)-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0191] Example 39. Preparation of *rac*-Ketamine Tolmetinate from *rac*-Ketamine Hydrochloride and Tolmetin Sodium Dihydrate.

[0192] *rac*-Ketamine tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of *rac*-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0193] Example 40. Preparation of *rac*-Ketamine Fenoprofenate from *rac*-Ketamine Hydrochloride and Fenoprofen Calcium Trihydrate.

[0194] *rac*-Ketamine fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884 g, 0.50 mmol) and of *rac*-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a

suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0195] Example 41. Preparation of *rac*-Ketamine Oxaprozinate from *rac*-Ketamine Hydrochloride and Oxaprozin.

[0196] *rac*-Ketamine oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0197] Example 42. Preparation of *rac*-Ketamine Difunisalate from *rac*-Ketamine Hydrochloride and Difunisal.

[0198] *rac*-Ketamine difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0199] **Example 42. Preparation of *rac*-Ketamine Loxoprofenate from *rac*-Ketamine Hydrochloride and Loxoprofen.**

[0200] *rac*-Ketamine loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0201] **Example 43. Preparation of (*S*)-Ketamine Ibuprofenate from (*S*)-Ketamine Hydrochloride and Ibuprofen.**

[0202] (*S*)-Ketamine ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0203] **Example 44. Preparation of (*S*)-Ketamine Acetylsalicylate from (*S*)-Ketamine Hydrochloride and Acetylsalicylic Acid.**

[0204] (*S*)-Ketamine acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a

minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal amount of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0205] Example 45. Preparation of (*S*)-Ketamine Salicylate from (*S*)-Ketamine Hydrochloride and Sodium Salicylate.

[0206] (*S*)-Ketamine Salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and of *(S)*-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0207] Example 46. Preparation of (*S*)-Ketamine Indomethacinate from (*S*)-Ketamine Hydrochloride and Indomethacin.

[0208] (*S*)-Ketamine indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0209] Example 47. Preparation of (*S*)-Ketamine Naproxenate from (*S*)-Ketamine Hydrochloride and Naproxen Sodium.

[0210] (*S*)-Ketamine Naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of (*S*)-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0211] Example 48. Preparation of (*S*)-Ketamine Etodolate from (*S*)-Ketamine Hydrochloride and Etodolac.

[0212] (*S*)-Ketamine etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0213] Example 49. Preparation of (*S*)-Ketamine Sulindate from (*S*)-Ketamine Hydrochloride and Sulindac.

[0214] (*S*)-Ketamine sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to

approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0215] Example 50. Preparation of (*S*)-Ketamine (S)-Ketoprofenate from (*S*)-Ketamine Hydrochloride and (*S*)-Ketoprofen.

[0216] (*S*)-Ketamine (*S*)-ketoprofenate may be prepared using the following synthetic scheme. *(S)*-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0217] Example 51. Preparation of (*S*)-Ketamine Suprofenate from (*S*)-Ketamine Hydrochloride and Suprofen.

[0218] (*S*)-Ketamine suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic suprofenate solution. The resulting solution is stirred and total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0219] Example 52. Preparation of (*S*)-Ketamine (*S*)-Flurbiprofenate from (*S*)-Ketamine Hydrochloride and (*S*)-Flurbiprofen.

[0220] (*S*)-Ketamine (*S*)-flurbiprofenate may be prepared using the following synthetic scheme. *(S)*-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0221] Example 53. Preparation of (*S*)-Ketamine Tolmetinate from (*S*)-Ketamine Hydrochloride and Tolmetin Sodium Dihydrate.

[0222] (*S*)-Ketamine tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of (*S*)-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0223] Example 54. Preparation of (*S*)-Ketamine Fenoprofenate from (*S*)-Ketamine Hydrochloride and Fenoprofen Calcium Trihydrate.

[0224] (*S*)-Ketamine Fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884 g, 0.50 mmol) and of (*S*)-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic

layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0225] Example 55. Preparation of (*S*)-Ketamine Oxaprozinate from (*S*)-Ketamine Hydrochloride and Oxaprozin.

[0226] (*S*)-Ketamine oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0227] Example 56. Preparation of (*S*)-Ketamine Difunisalate from (*S*)-Ketamine Hydrochloride and Difunisal.

[0228] (*S*)-Ketamine difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation.

[0229] Example 55. Preparation of (*S*)-Ketamine Loxoprofenate from (*S*)-Ketamine Hydrochloride and Loxoprofen.

[0230] (*S*)-Ketamine loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. (*S*)-Ketamine hydrochloride (0.2742 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0231] Example 56. Preparation of (*S*)-Ketamine Diclofenate from of (*S*)-Ketamine Hydrochloride and Sodium Diclofenac.

[0232] (*S*)-Ketamine diclofenate may be prepared using the following synthetic scheme. Aqueous solutions of sodium diclofenac (0.3181 g, 1.00 mmol) and of (*S*)-ketamine hydrochloride (0.2742 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0233] Example 57. Preparation of *rac*-Methadone Ibuprofenate from *rac*-Methadone Hydrochloride and Ibuprofen.

[0234] *rac*-Methadone ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume is reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL).

The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0235] Example 58. Preparation of *rac*-Methadone Acetylsalicylate from *rac*-Methadone Hydrochloride and Acetylsalicylic Acid.

[0236] *rac*-Methadone acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0237] Example 59. Preparation of *rac*-Methadone Salicylate from *rac*-Methadone Hydrochloride and Sodium Salicylate.

[0238] *rac*-Methadone salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and of *rac*-methadone hydrochloride (0.3459 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0239] Example 60. Preparation of *rac*-Methadone Indomethacinate from *rac*-Methadone Hydrochloride and Indomethacin.

[0240] *rac*-Methadone indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol)

dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0241] Example 61. Preparation of *rac*-Methadone Naproxenate from *rac*-Methadone Hydrochloride and Naproxen Sodium.

[0242] *rac*-Methadone naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of *rac*-methadone hydrochloride (0.3459 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0243] Example 62. Preparation of *rac*-Methadone Etodolate from *rac*-Methadone Hydrochloride and Etodolac.

[0244] *rac*-Methadone etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0245] **Example 63. Preparation of *rac*-Methadone Sulindate from *rac*-Methadone Hydrochloride and Sulindac.**

[0246] *rac*-Methadone sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0247] **Example 64. Preparation of *rac*-Methadone (*S*)-Ketoprofenate from *rac*-Methadone Hydrochloride and (*S*)-Ketoprofen.**

[0248] *rac*-Methadone (*S*)-ketoprofen may be prepared using the following synthetic scheme. (*S*)-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0249] **Example 65. Preparation of *rac*-Methadone Suprofenate from *rac*-Methadone Hydrochloride and Suprofen.**

[0250] *rac*-Methadone suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal

volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0251] Example 66. Preparation of *rac*-Methadone (*S*)-Flurbiprofenate from *rac*-Methadone Hydrochloride and (*S*)-Flurbiprofen.

[0252] *rac*-Methadone (*S*)-flurbiprofen may be prepared using the following synthetic scheme. (*S*)-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0253] Example 67. Preparation of *rac*-Methadone Tolmetinate from *rac*-Methadone Hydrochloride and Tolmetin Sodium Dihydrate.

[0254] *rac*-Methadone tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0255] **Example 68. Preparation of *rac*-Methadone Fenoprofenate from *rac*-Methadone Hydrochloride and Fenoprofen Calcium Trihydrate.**

[0256] *rac*-Methadone fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884 g, 0.50 mmol) and of *rac*-methadone hydrochloride (0.3459 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0257] **Example 69. Preparation of *rac*-Methadone Oxaprozinate from *rac*-Methadone Hydrochloride and Oxaprozin.**

[0258] *rac*-Methadone oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0259] **Example 70. Preparation of *rac*-Methadone Difunisalate from *rac*-Methadone Hydrochloride and Difunisal.**

[0260] *rac*-Methadone difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume

reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0261] Example 71. Preparation of *rac*-Methadone Loxoprofenate from *rac*-Methadone Hydrochloride and Loxoprofen.

[0262] *rac*-Methadone loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) is dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *rac*-Methadone hydrochloride (0.3459 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0263] Example 72. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Ibuprofenate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Ibuprofen.

[0264] 5*R*,9*R*,13*S*,14*R*-Hydrocodone ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-hydrocodone bitartrate hemipentahydrate (0.4549 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0265] Example 73. **Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Acetylsalicylate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Acetylsalicylic Acid.**

[0266] 5*R*,9*R*,13*S*,14*R*-Hydrocodone acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0267] Example 74. **Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Salicylate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Sodium Salicylate.**

[0268] 5*R*,9*R*,13*S*,14*R*-Hydrocodone salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and of 5*R*,9*R*,13*S*,14*R*-hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0269] Example 75. **Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Indomethacinate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Indomethacin.**

[0270] 5*R*,9*R*,13*S*,14*R*-Hydrocodone indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) dissolved in a

minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0271] Example 76. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Naproxenate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Naproxen Sodium.

[0272] 5*R*,9*R*,13*S*,14*R*-Hydrocodone naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of 5*R*,9*R*,13*S*,14*R*-hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0273] Example 77. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Etodolate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Etodolac.

[0274] 5*R*,9*R*,13*S*,14*R*-Hydrocodone etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with

diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0275] Example 78. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Sulindate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Sulindac.

[0276] 5*R*,9*R*,13*S*,14*R*-Hydrocodone sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal amount of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0277] Example 79. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone (*S*)-Ketoprofenate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and (*S*)-Ketoprofen.

[0278] 5*R*,9*R*,13*S*,14*R*-Hydrocodone (*S*)-ketoprofenate may be prepared using the following synthetic scheme. (*S*)-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0279] **Example 80. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Suprofenate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Suprofen.**

[0280] 5*R*,9*R*,13*S*,14*R*-Hydrocodone suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) is dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0281] **Example 81. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone (*S*)-Flurbiprofenate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and (*S*)-Flurbiprofen.**

[0282] 5*R*,9*R*,13*S*,14*R*-Hydrocodone (*S*)-flurbiprofenate may be prepared using the following synthetic scheme. (*S*)-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0283] **Example 82. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Tolmetinate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Tolmetin Sodium Dihydrate.**

[0284] 5*R*,9*R*,13*S*,14*R*-Hydrocodone tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0285] **Example 83. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Fenoprofenate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Fenoprofen Calcium Trihydrate.**

[0286] 5*R*,9*R*,13*S*,14*R*-Hydrocodone fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884g, 0.50 mmol) and of 5*R*,9*R*,13*S*,14*R*-hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0287] **Example 84. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Oxaprozinate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Oxaprozin.**

[0288] 5*R*,9*R*,13*S*,14*R*-Hydrocodone oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *5R,9R,13S,14R*-Hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution.

The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0289] Example 85. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Difunisalate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Difunisal.

[0290] 5*R*,9*R*,13*S*,14*R*-Hydrocodone difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. *5R,9R,13S,14R*-Hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0291] Example 86. Preparation of 5*R*,9*R*,13*S*,14*R*-Hydrocodone Loxoprofenate from 5*R*,9*R*,13*S*,14*R*-Hydrocodone Bitartrate Hemipentahydrate and Loxoprofen.

[0292] 5*R*,9*R*,13*S*,14*R*-Hydrocodone loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. 5*R*,9*R*,13*S*,14*R*-Hydrocodone bitartrate hemipentahydrate (0.4945 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic

layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0293] Example 87. Preparation of 5*R*,6S,9*R*,13*S*,14*R*-Codeine Ibuprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Ibuprofen.

[0294] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0295] Example 88. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Acetylsalicylate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Acetylsalicylic Acid.

[0296] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) is dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0297] Example 89. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Salicylate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Sodium Salicylate.

[0298] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and of codeine sulfate (0.3484 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0299] Example 90. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Indomethacinate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Indomethacin.

[0300] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) is dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0301] Example 91. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Naproxenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Naproxen Sodium.

[0302] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of codeine sulfate (0.3484 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0303] Example 92. **Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Etodolate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Etodolac.**

[0304] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0305] Example 93. **Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulindate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Sulindac.**

[0306] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0307] Example 94. **Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine (*S*)-Ketoprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and (*S*)-Ketoprofen.**

[0308] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine (*S*)-ketoprofenate may be prepared using the following synthetic scheme. (*S*)-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00

mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0309] Example 95. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Suprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Suprofen.

[0310] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The condensed solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0311] Example 96. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine (*S*)-Flurbiprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and (*S*)-Flurbiprofen.

[0312] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine (*S*)-flurbiprofenate may be prepared using the following synthetic scheme. (*S*)-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether

(4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0313] Example 97. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Tolmetinate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Tolmetin Sodium Dihydrate.

[0314] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of codeine sulfate (0.3484 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0315] Example 98. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Fenoprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Fenoprofen Calcium Trihydrate.

[0316] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884 g, 0.50 mmol) and of codeine sulfate (0.3484 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0317] Example 99. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Oxaprozinate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Oxaprozin.

[0318] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total

volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0319] Example 100. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Difunisalate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Difunisal.

[0320] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0321] Example 101. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Loxoprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine Sulfate and Loxoprofen.

[0322] 5*R*,6*S*,9*R*,13*S*,14*R*-Codeine loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Codeine sulfate (0.3484 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0323] **Example 102. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Ibuprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Ibuprofen.**

[0324] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0325] **Example 103. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Acetylsalicylate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Acetylsalicylic Acid.**

[0326] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0327] **Example 104. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Salicylate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Sodium Salicylate.**

[0328] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and

of morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0329] Example 105. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Indomethacinate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Indomethacin.

[0330] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0331] Example 106. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Naproxenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Naproxen Sodium.

[0332] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0333] **Example 107. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Etodolate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Etodolac.**

[0334] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation.

[0335] **Example 108. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulindate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Sulindac.**

[0336] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume is reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0337] **Example 109. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine (*S*)-Ketoprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and (*S*)-Ketoprofen.**

[0338] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine (*S*)-ketoprofenate may be prepared using the following synthetic scheme. (*S*)-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00

mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume is reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0339] Example 110. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Suprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Suprofen.

[0340] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0341] Example 111. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine (*S*)-Flurbiprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and (*S*)-Flurbiprofen.

[0342] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine (*S*)-flurbiprofenate may be prepared using the following synthetic scheme. (*S*)-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated

solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0343] Example 112. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Tolmetinate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Tolmetin Sodium Dihydrate.

[0344] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0345] Example 113. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Fenoprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Fenoprofen Calcium Trihydrate.

[0346] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884 g, 0.50 mmol) and of morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0347] Example 114. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Oxaprozinate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Oxaprozin.

[0348] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal

volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0349] Example 115. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Difunisalate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Difunisal.

[0350] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0351] Example 116. Preparation of 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Loxoprofenate from 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine Sulfate Pentahydrate and Loxoprofen.

[0352] 5*R*,6*S*,9*R*,13*S*,14*R*-Morphine loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Morphine sulfate pentahydrate (0.3794 g, 0.50 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is

stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0353] Example 117. Preparation of Levorphanol Ibuprofenate from Levorphanol Tartrate Dihydrate and Ibuprofen.

[0354] Levorphanol ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. A solution of (*l*)-3-hydroxy-N-methylmorphinan (herein referred to as levorphanol) tartrate dihydrate (0.4435 g, 1.00 mmol) is prepared in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0355] Example 118. Preparation of Levorphanol Acetylsalicylate from Levorphanol Tartrate Dihydrate and Acetylsalicylic Acid.

[0356] Levorphanol acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0357] **Example 119. Preparation of Levorphanol Salicylate from Levorphanol Tartrate Dihydrate and Sodium Salicylate.**

[0358] Levorphanol salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and of levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0359] **Example 120. Preparation of Levorphanol Indomethacinate from Levorphanol Tartrate Dihydrate and Indomethacin.**

[0360] Levorphanol indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0361] **Example 121. Preparation of Levorphanol Naproxenate from Levorphanol Tartrate Dihydrate and Naproxen Sodium.**

[0362] Levorphanol naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic

layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0363] Example 122. Preparation of Levorphanol Etodolate from Levorphanol Tartrate Dihydrate and Etodolac.

[0364] Levorphanol etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0365] Example 123. Preparation of Levorphanol Sulindate from Levorphanol Tartrate Dihydrate and Sulindac.

[0366] Levorphanol sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0367] Example 124. Preparation of Levorphanol (*S*)-Ketoprofenate from Levorphanol Tartrate Dihydrate and (*S*)-Ketoprofen.

[0368] Levorphanol (*S*)-ketoprofenate may be prepared using the following synthetic scheme. (*S*)-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0369] Example 125. Preparation of Levorphanol Suprofenate from Levorphanol Tartrate Dihydrate and Suprofen.

[0370] Levorphanol suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0371] Example 126. Preparation of Levorphanol (*S*)-Flurbiprofenate from Levorphanol Tartrate Dihydrate and (*S*)-Flurbiprofen.

[0372] Levorphanol (*S*)-flurbiprofenate may be prepared using the following synthetic scheme. (*S*)-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and

combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0373] Example 127. Preparation of Levorphanol Tolmetinate from Levorphanol Tartrate Dihydrate and Tolmetin Sodium Dihydrate.

[0374] Levorphanol tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0375] Example 128. Preparation of Levorphanol Fenoprofenate from Levorphanol Tartrate Dihydrate and Fenoprofen Calcium Trihydrate.

[0376] Levorphanol fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884 g, 0.50 mmol) and of levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0377] Example 129. Preparation of Levorphanol Oxaprozinate from Levorphanol Tartrate Dihydrate and Oxaprozin.

[0378] Levorphanol oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal

volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0379] Example 130. Preparation of Levorphanol Difunisalate from Levorphanol Tartrate Dihydrate and Difunisal.

[0380] Levorphanol difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0381] Example 131. Preparation of Levorphanol Loxoprofenate from Levorphanol Tartrate Dihydrate and Loxoprofen.

[0382] Levorphanol loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume is reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90

mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0383] Example 132. Preparation of Levorphanol Diclofenate from Levorphanol Tartrate Dihydrate and Sodium Diclofenac.

[0384] Levorphanol diclofenate may be prepared using the following synthetic scheme. Aqueous solutions of sodium diclofenac (0.3181 g, 1.00 mmol) and of levorphanol tartrate dihydrate (0.4435 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0385] Example 133. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Ibuprofenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Ibuprofen.

[0386] 5*R*,9*R*,13*R*,14*S*-Oxycodone ibuprofenate may be prepared using the following synthetic scheme. Ibuprofen (0.2063 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ibuprofenate solution. The resulting solution is stirred and the total volume is reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0387] Example 134. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Acetylsalicylate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Acetylsalicylic Acid.

[0388] 5*R*,9*R*,13*R*,14*S*-Oxycodone acetylsalicylate may be prepared using the following synthetic scheme. Acetylsalicylic acid (0.3003 g, 1.00 mmol) dissolved in a

minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic acetylsalicylate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0389] Example 135. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Salicylate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Sodium Salicylate.

[0390] 5*R*,9*R*,13*R*,14*S*-Oxycodone salicylate may be prepared using the following synthetic scheme. Aqueous solutions of sodium salicylate (0.1601 g, 1.00 mmol) and of oxycodone hydrochloride (0.3518 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0391] Example 136. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Indomethacinate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Indomethacin.

[0392] 5*R*,9*R*,13*R*,14*S*-Oxycodone indomethacinate may be prepared using the following synthetic scheme. Indomethacin (0.3578 g, 1.00 mmol) dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic indomethacinate solution. The resulting solution is stirred and the total volume is reduced to approximately 30 mL. The solution is transferred to a separatory funnel and the desired product extracted with diethyl ether

(4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0393] Example 137. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Naproxenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Naproxen Sodium.

[0394] 5*R*,9*R*,13*R*,14*S*-Oxycodone naproxenate may be prepared using the following synthetic scheme. Aqueous solutions of naproxen sodium (0.2522 g, 1.00 mmol) and of oxycodone hydrochloride (0.3518 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0395] Example 137. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Etodolate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Etodolac.

[0396] 5*R*,9*R*,13*R*,14*S*-Oxycodone etodolate may be prepared using the following synthetic scheme. Etodolac (0.2874 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic etodolate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0397] Example 138. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Sulindate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Sulindac.

[0398] 5*R*,9*R*,13*R*,14*S*-Oxycodone sulindate may be prepared using the following synthetic scheme. Sulindac (0.3564 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a

minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic sulindate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0399] Example 139. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone (*S*)-Ketoprofenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and (*S*)-Ketoprofen.

[0400] **5*R*,9*R*,13*R*,14*S*-**Oxycodone (*S*)-ketoprofenate may be prepared using the following synthetic scheme. (*S*)-Ketoprofen (0.2543 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic ketoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0401] Example 140. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Suprofenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Suprofen.

[0402] 5*R*,9*R*,13*R*,14*S*-Oxycodone suprofenate may be prepared using the following synthetic scheme. Suprofen (0.2603 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic suprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a

separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0403] Example 141. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone (*S*)-Flurbiprofenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and (*S*)-Flurbiprofen.

[0404] 5*R*,9*R*,13*R*,14*S*-Oxycodone (*S*)-flurbiprofenate may be prepared using the following synthetic scheme. (*S*)-Flurbiprofen (0.2443 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic flurbiprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0405] Example 142. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Tolmetinate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Tolmetin Sodium Dihydrate.

[0406] 5*R*,9*R*,13*R*,14*S*-Oxycodone tolmetinate may be prepared using the following synthetic scheme. Aqueous solutions of tolmetin sodium dihydrate (0.3153 g, 1.00 mmol) and of oxycodone hydrochloride (0.3518 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0407] Example 143. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Fenoprofenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Fenoprofen Calcium Trihydrate.

[0408] 5*R*,9*R*,13*R*,14*S*-Oxycodone fenoprofenate may be prepared using the following synthetic scheme. Aqueous solutions of fenoprofen calcium trihydrate (0.2884 g, 0.50 mmol) and of oxycodone hydrochloride (0.3518 g, 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0409] Example 144. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Oxaprozinate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Oxaprozin.

[0410] 5*R*,9*R*,13*R*,14*S*-Oxycodone oxaprozinate may be prepared using the following synthetic scheme. Oxaprozin (0.2933 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic oxaprozinate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0411] Example 145. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Difunisalate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Difunisal.

[0412] 5*R*,9*R*,13*R*,14*S*-Oxycodone difunisalate may be prepared using the following synthetic scheme. Difunisal (0.2502 g, 1.00 mmol) dissolved in a minimal volume of ethanol is combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the

ethanolic difunisalate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0413] Example 146. Preparation of 5*R*,9*R*,13*R*,14*S*-Oxycodone Loxoprofenate from 5*R*,9*R*,13*R*,14*S*-Oxycodone Hydrochloride and Loxoprofen.

[0414] 5*R*,9*R*,13*R*,14*S*-Oxycodone loxoprofenate may be prepared using the following synthetic scheme. Loxoprofen (0.2463 g, 1.00 mmol) is dissolved in a minimal volume of ethanol and combined with potassium hydroxide (0.05611 g, 1.00 mmol) dissolved in a minimal volume of ethanol and stirred for 1 hour. Oxycodone hydrochloride (0.3518 g, 1.00 mmol) is dissolved in a minimal volume of water and combined with the ethanolic loxoprofenate solution. The resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a separatory funnel and the desired product extracted with diethyl ether (4 × 90 mL). The organic layers are combined and the solvent removed by rotary evaporation. The product is dried under vacuum overnight.

[0415] Example 147. Particle Size Resulting When a Propoxyphene Diclofenate Solution is Added to Hydrochloric Acid

[0416] Particle size of a methanolic solution of propoxyphene diclofenate (61 mg/mL, 0.096 mmol/mL, 25 mL) was monitored for 2.5 hours by adding this solution to HCl (0.1 *N*, 25 mL). Measurements were obtained using a Sympatec HELOS model KF particle sizer with SUCELL and R5 lens (0.5 – 875 μm), pump, and stirrer speeds set to 50 % of the maximum value. The SUCELL was filled with water and reference measurements were acquired before adding an appropriate amount of propoxyphene diclofenate solution for an approximate optical concentration of 10 % at timepoints of 15, 45, 75, 120, and 150 minutes. The results are tabulated in Table 15.

[0417] Table 15. Results for Propoxyphene Diclofenate (61 mg/mL) in MeOH

Timepoint (minutes)	Mean (μm)	≤ 50% (μm)	≤ 90% (μm)
15	152.4	141.2	287.9
45	155.5	143.0	293.9
75	161.7	140.5	308.6
120	149.2	135.4	286.3
150	124.2	110.2	238.4

[0418] Example 148. Particle Size Resulting When A Propoxyphene Diclofenate Formulation is Added to Hydrochloric Acid

[0419] A propoxyphene diclofenate solution was prepared by adding propoxyphene diclofenate (12.5 mg, 0.020 mmol) to the contents of a placebo 50 mg capsule containing a dispersant and a solubilizer. The particle size of this solution was monitored for about 2 hours by adding the solution of propoxyphene diclofenate to HCl (0.1 *N*, 25 mL). Measurements were obtained using a Sympatec HELOS model KF particle sizer with SUCELL and R5 lens (0.5 – 875 um), pump and stirrer speeds set to 50% of the maximum value. The SUCELL was filled with water and reference measurements were acquired before adding an appropriate amount of propoxyphene diclofenate solution for an approximate optical concentration of 10 % at timepoints of 5, 10, 20, 30, 40, 60, 80, and 100 minutes. The data are shown in Table 16.

[0420] Table 16. Particle Size Results for Propoxyphene Diclofenate Formulation

Timepoint (minutes)	Mean (μm)	≤ 50% (μm)	≤ 90% (μm)
5	6.6	5.7	11.7
10	6.6	5.6	11.6
20	6.2	5.6	11.2
30	6.6	5.6	11.4
40	6.1	5.5	10.9
60	6.1	5.5	10.9
80	6.0	5.4	10.7
100	6.8	5.6	11.4

[0421] Example 149. Particle Size Resulting When A Propoxyphene Diclofenate Formulation is Added to Hydrochloric Acid

[0422] A propoxyphene diclofenate solution was prepared by adding propoxyphene diclofenate (25 mg, 0.039 mmol) to the contents of a placebo 50 mg capsule containing a dispersant and a solubilizer. The particle size of this solution was monitored for about 2 hours by adding the solution of propoxyphene diclofenate to HCl (0.1 *N*, 25 mL). Measurements were obtained using a Sympatec HELOS model KF particle sizer with SUCELL and R5 lens (0.5 – 875 μm), pump, and stirrer speeds set to 50 % of the maximum value. The SUCELL was filled with water and reference measurements were acquired before adding an appropriate amount of Propoxyphene Diclofenate solution for an approximate optical concentration of 10 % at timepoints of 5, 10, 20, 30, 40, 60, 80, and 100 minutes. The data are shown in Table 17.

[0423] Table 17. Particle Size Results for Propoxyphene Diclofenate Formulation

Timepoint (minutes)	Mean (μm)	≤ 50% (μm)	≤ 90% (μm)
5	8.8	6.9	17.5
10	8.0	6.5	15.1
20	7.4	6.1	13.8
30	7.5	6.0	13.5
40	7.1	5.9	12.9
60	6.9	5.8	12.4
80	7.1	5.7	12.3
100	6.8	5.7	12.1

[0424] **Example 150. Particle Size Resulting When A Propoxyphene Diclofenate Formulation is Added to Hydrochloric Acid**

[0425] A propoxyphene diclofenate solution was prepared by adding propoxyphene diclofenate (40 mg, 0.063 mmol) to the contents of a placebo 50 mg capsule containing a dispersant and a solubilizer. The particle size of this solution was

monitored for about 2 hours by adding the solution of propoxyphene diclofenate to HCl (0.1 *N*, 25 mL). Measurements were obtained using a Sympatec HELOS model KF particle sizer with SUCELL and R5 lens (0.5 - 875 mm), pump, and stirrer speeds set to 50 % of the maximum value. The SUCELL was filled with water and reference measurements were acquired before adding an appropriate amount of propoxyphene diclofenate solution for an approximate optical concentration of 10 % at timepoints of 20, 40, 60, 90, and 120 minutes. The data are shown in Table 18.

[0426] Table 18. Particle Size Results for Propoxyphene Diclofenate Formulation

Timepoint (minutes)	Mean (μm)	≤ 50 % (μm)	≤ 90 % (μm)
20	9.1	7.0	18.0
40	8.8	6.7	17.3
60	8.5	6.4	16.0
90	7.9	6.1	14.8
120	7.8	6.0	14.4

[0427] **Example 151. Particle Size Resulting When A Propoxyphene Diclofenate Formulation is Added to Hydrochloric Acid**

[0428] A propoxyphene diclofenate solution was prepared by adding propoxyphene diclofenate (50 mg, 0.079 mmol) to the contents of a placebo 50 mg capsule containing a dispersant and a solubilizer. The particle size of this solution was monitored for about 2 hours by adding the solution of propoxyphene diclofenate to HCl (0.1 *N*, 25 mL). Measurements were obtained using a Sympatec HELOS model KF particle sizer with SUCELL and R5 lens (0.5 - 875 mm), pump, and stirrer speeds set to 50 % of the maximum value. The SUCELL was filled with water and reference measurements were acquired before adding an appropriate amount of propoxyphene diclofenate solution for an approximate optical concentration of 10 % at timepoints of 5, 10, 20, 30, 40, 60, 80, and 120 minutes. The data are shown in Table 19.

[0429] Table 19. Particle Size Results for Propoxyphene Diclofenate Formulation

Timepoint (minutes)	Mean (μm)	≤ 50% (μm)	≤ 90% (μm)
5	9.1	7.0	17.9
10	9.4	6.9	18.4
20	9.1	6.6	17.4
30	8.6	6.3	16.1
40	8.3	6.1	15.4
60	8.5	5.9	15.1
80	8.0	5.8	14.3
120	7.8	5.7	14.2

[0430] **Example 152. Solubility When Propoxyphene Diclofenate is Added to Water at Various pH Values**

[0431] Propoxyphene diclofenate solutions were prepared by adding propoxyphene diclofenate (approx. 48 mg, 0.076 mmol) to dissolution vessels containing water (400 mL) at pH of 3, 5, 7, 9, and 11 and equilibrated at 36.8 °C. The solutions were stirred by paddles at 150 RPM for approximately 12 hours. Final sample solutions were prepared by diluting 12.5 mL of the propoxyphene diclofenate solution from each vessel filtered through a 0.45 μm Nylon filter to 50.0 mL with methanol. Five standard solutions of propoxyphene diclofenate were prepared at concentrations ranging from 0.00091 to 0.02914 mg/mL. The standards and sample preparations were measured at 282 nm in a 1 cm cell using a UV spectrophotometer. The results were determined from the linearity curve generated from the standard data. The data are shown in Table 20.

[0432] Table 20. Solubility Results for Propoxyphene Diclofenate as a Function of pH

pH	mg Dissolved from 48 mg Solution	mg/mL Dissolved	% Dissolved
3	0.004	1.0528×10^{-5}	0.009
5	36.005	0.09	74.878
7	36.644	0.0916	75.677

9	34.018	0.08504	71.168
11	18.700	0.04676	39.395

[0433] **Example 153. Solubility of Propoxyphene Diclofenate in Polyethylene Glycol**

[0434] The total solubility of propoxyphene diclofenate in polyethylene glycol 400 was determined to exceed 670 mg/mL. The solubility was determined by UV detection using a standard solution (0.049 mmol/L).

[0435] Example 154. Preparation of (2*S*,3*R*)-(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate Diclofenate from Sodium Diclofenac and (2*S*,3*R*)-(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate (Propoxyphene) Hydrochloride

[0436] Sodium diclofenac (133.7 g, 0.4203 mol) was dissolved in water (2500 mL) at about 50 °C with mechanical stirring. To this a 50 °C solution of (2*S*,3*R*)-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate hydrochloride (158.6 g, 0.4219 mol) in water (600 mL) was slowly added while vigorously stirring the mixture with a mechanical stirrer and maintaining the temperature at about 50 °C. A thick sticky white precipitate formed as the mixture was stirred. The reaction was monitored by HPLC to calculate the amount of propoxyphene remaining in solution. When the reaction was considered complete, as evidence by the disappearance of propoxyphene from solution, the solution was decanted, and the solid product washed with multiple aliquots of water (about 2000 mL) at 50 °C with mechanical stirring until HPLC confirmed only low levels of unreacted sodium diclofenac present. The solid material was then dissolved in a minimal amount of acetone and the acetone subsequently removed by rotary evaporation under vacuum to yield a white solid. The white solid was then removed from the flask and spread over the bottom of a crystallizing dish which is placed in a vacuum oven for prolonged drying at 30 °C to remove any odor of residual acetone. Yield of the title compound was 239.2 g (0.3763 mol; 89.5%).

[0437] Example 155. Preparation of (2*S*,3*R*)-(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate Diclofenate from Sodium Diclofenac and (2*S*,3*R*)-(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate (Propoxyphene) Hydrochloride

[0438] Propoxyphene hydrochloride (117.0 g, 0.3112 mol) was dissolved in water (1500 mL) at about 50°C with mechanical stirring. To this a 50°C solution of sodium diclofenac (108.2g, 0.34 mol) in water (2000 mL) was slowly added while vigorously stirring the mixture with a mechanical stirrer and maintaining the temperature at about 50°C. A thick sticky white precipitate formed as the solution was stirred. Completeness of reaction was confirmed by HPLC to determine the amount of unreacted propoxyphene hydrochloride remaining in solution (about 1 mg/mL remained). The reaction was considered complete, the solution was decanted, and the solid product washed with numerous aliquots of water (about 300 mL for each washing) at about 50°C with mechanical stirring until HPLC confirmed only low levels of unreacted sodium diclofenate remained (about 0.2 mg/mL). The solid material was then dissolved in a minimal amount of acetone and the acetone subsequently removed by rotary evaporation to yield a white solid. The white solid was then removed from the flask and spread over the bottom of a crystallizing dish which was placed in a vacuum oven for prolonged drying at 30°C to remove residual acetone. Acetone removal was considered complete when no odor of residual acetone remained. Yield of the title compound was 150.9 g (0.2374 mol; 76.3%).

[0439] Example 156. Preparation of (2*S*,3*R*)-(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate Diclofenate from Potassium Diclofenac and (2*S*,3*R*)-(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate (Propoxyphene) Hydrochloride

[0440] Potassium diclofenac (335.2 g, 1.003 mol) was dissolved in water (2000 mL) at about 50°C with mechanical stirring. To this a 50°C solution of (2*S*,3*R*)-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate hydrochloride (376.6 g, 1.002 mol) in water (700 mL) was slowly added while vigorously stirring the mixture with a mechanical stirrer and maintaining the temperature at about 50°C. A thick

sticky white precipitate formed as the solution was stirred over several hours. Completeness of reaction was confirmed by HPLC to determine the amount of unreacted propoxyphene hydrochloride remaining in solution (about 1 mg/mL remained). The reaction was considered complete when about 1 mg/mL propoxyphene hydrochloride remained in solution. The solvent was decanted, and the solid product washed with numerous aliquots of water (about 500 mL for each washing) at about 50°C with mechanical stirring until HPLC confirmed only low levels of unreacted sodium diclofenate remained (about 0.2 mg/mL). The solid material was then dissolved in a minimal amount of acetone and the acetone subsequently removed by rotary evaporation to yield a white solid. The white solid was then removed from the flask and spread over the bottom of a crystallizing dish which was placed in a vacuum oven for prolonged drying at 30°C to remove residual acetone. Acetone removal was considered complete when no odor of residual acetone remained. Yield of the title compound was 613.2 g (0.9647 mol; 96.3%).

[0441] Example 157. Analysis of Washings of Propoxyphene Diclofenate Synthesis Using High Pressure Liquid Chromatography (HPLC)

[0442] During the synthesis of propoxyphene diclofenate in the foregoing examples, the product was washed with water to remove excess diclofenac (sodium or potassium). The levels of diclofenac salts were monitored to determine the reaction end point by HPLC according to the following procedure.

[0443] HPLC was performed with the HP1100 system (Hewlett Packard, Palo Alto, CA). The method utilized a 4.6 × 150 mm C_{18} column (Waters Corporation, Milford, MA) maintained at room temperature. The mobile phase was gradient controlled, consisting of Mobile Phase A (MP_A), a 90:10 mixture of water (4 drops trifluoroacetic acid (TFA) per 900 mL); and Mobile Phase B (MP_B), a 70:30 mixture of acetonitril:water. The gradient program was set as follows:

Time (min)	% MP_A	% MP_B
0.0	95.0	95.0
30.0	5.0	95.0

31.0	5.0	95.0
32.0	95.0	5.0

[0444] The flow rate was maintained at 1.0 mL/minute. Standards and sample solutions were prepared in water at concentrations of 0.3, 0.6, and 1.0 mM. Injection volume for sample and standard preparations (diclofenac potassium (Yung Zip); propoxyphene HCl (Mallinckrodt)) was 10 μL and run time was about 32 minutes. UV detection was performed at 217 nm. The chromatographic data peak areas were collected and analyzed using Millenium[32] chromatography software (Waters Corporation, Milford, MA) to generate the %w/w assay values for the samples.

[0445] Example 158. Analysis of the Aqueous Mother Liquor and Subsequent Washings During Propoxyphene Diclofenate Synthesis Using High Pressure Liquid Chromatography

[0446] During the synthesis of propoxyphene diclofenate as described in the foregoing examples the reaction was considered complete once the reaction mixture contained an acceptably low level of propoxyphene as determined by HPLC. When the reaction was complete, the aqueous mother liquor was decanted and the product washed with numerous aqueous rinses to remove excess diclofenac (sodium or potassium). Using an HPLC analysis according to the following procedure, the propoxyphene and diclofenac levels were monitored during the reaction to determine the end point of the reaction, and the point when sufficient washing had been accomplished.

[0447] For each of the procedures above, HPLC was performed with the HP1100 system (Hewlett Packard, Palo Alto, CA). The method utilized a 4.6 × 150 mm C_{18} column (Waters Corporation, Milford, MA) maintained at room temperature. The mobile phase was gradient controlled, consisting of Mobile Phase A; a 90:10 mixture of water (4 drops trifluoroacetic acid (TFA) per 900 mL):acetonitrile, and Mobile Phase B; a 70:30 mixture of acetonitrile:water. The gradient program was set as follows:

Time (min)	% MP_A	% MP_B
0.0	95.0	95.0
30.0	5.0	95.0
31.0	5.0	95.0
32.0	95.0	5.0

[0448] The flow rate was maintained at 1.0 mL/minute. Standard and sample solutions were prepared in water at concentrations of 0.3, 0.6, and 1.0 mM. Injection volume for the sample and standard preparations (diclofenac potassium (Yung Zip); propoxyphene HCl (Mallinckrodt)) was 10 µL and runtime of the analysis was about 32 minutes. UV detection was performed at 217 nm. The chromatographic data peak areas were collected and analyzed using Millennium[32] chromatography software (Waters Corporation, Milford, MA) to generate the %w/w values for the samples.